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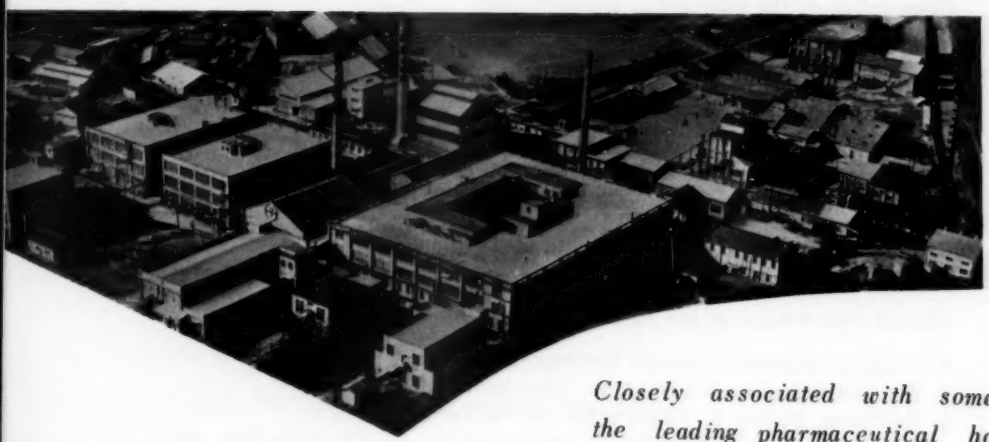

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THE PROBLEMS OF SO-CALLED "URO-GENITAL TRACHOMA"

Shozo OISHI and Masaki SENOO

Department of Ophthalmology, Yamaguchi Medical School

Introduction

The name of "Uro-genital Trachoma" has been used for a long time[1]. Many ophthalmologists believed in the existence of this condition, simply because some authors[2)3)4)] claimed to have discovered the Prowazek-Halberstaedter's inclusion bodies in the epithelium of mother's urethra or the cervical canal who had given birth to babies suffering from inclusion blennorrhea. Some[5)6)7)] succeeded in attempts to inoculate into the epithelia of the urethra or the cervical canal the materials containing inclusion bodies.

Okamura et al (1940) also reported that two healthy women had been successfully inoculated in the cervical canal with trachoma materials, and that after 220 days inclusion bodies have been demonstrated in its epithelia. Pathohistologically, they also found follicular infiltration in the subepithelial tissue which was about the same as that seen in trachoma. Therefore, they believe that inclusion blennorrhea is nothing more than a form of infantile trachoma.

Recently Abu-Jaubeh (1953) supported the concept that the inclusion body represents a living virus of uro-genital trachoma, on the basis that he could demonstrate the so-called inclusion bodies in 16 cases (14.2%) out of 112 trachomatous girls a Beirut.

From these reports it would be thought that the hotbed of trachoma is closely related to urogenital parts of the human body. Nevertheless, we have some doubts as to whether or not the etiologic cause of trachoma is the same as that of inclusion conjunctivitis in a new-born child which caused infection in the birth canal of the mother. We strongly feel that it is imperative to know the relationship between the conjunctival and the urogenital trachoma.

Material and Methods

We selected over 1000 out-patients at the Gynecological Clinic of Onoda Hospital in Yamaguchi Prefecture, Japan, where about 20 percent of the population is suffering from trachoma. They were so selected that they had never used antibiotics or sulfonmide, for these drugs are effective against the inclusion bodies and other eye organisms to modify the results. No special attempts were made to assess the age, neither was the disease of gynecology considered.

The materials were obtained by scraping very gently the mucosa of pars vaginalis and pars cervicalis of uterus and urethra with Cuscow's curette (No. 2) after washing with Cameleon's solution. The samples were then smeared directly upon the object glasses. They were examined by Giemsa's staining, Poleff's special stainning[10)] and

also by other methods. In this way, we could easily observe in the smears mucous epithelial cells and specific uro-genital micro-organisms as in the case of smears of the conjunctival sac.

Fig. 1 The ages of patients

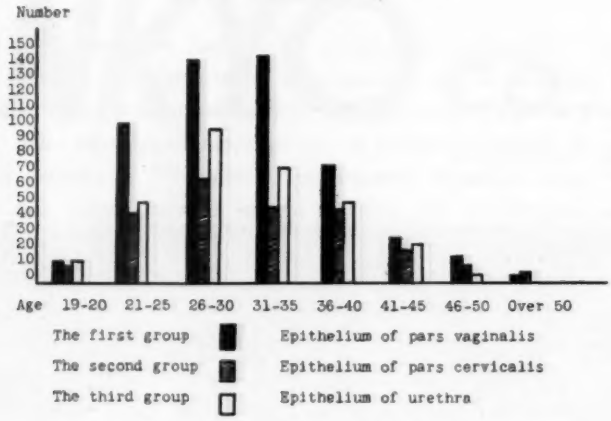


Table 1 The gynecological diagnasis of patients

Clinical diagnosis	I group	II group	III group	Total
1 Pregnancy	236	84	200	530
2 Contraception	96	34	27	157
3 Abortion	31	30	18	79
4 Retoflexion of uterus	54	9	7	70
5 Diseases of vagina	20	8	6	34
6 Endometritis	12	7	11	30
7 Salpingitis	9	5	7	21
8 Cystitis	6	3	4	13
9 Metropathia hemorrhagica	3	2	4	9
10 Condyloma acuminata	1	6	0	7
11 Periurethritis	0	0	3	3
12 Barthritis	0	2	0	2
13 Ulcus molle	1	0	0	1
14 Normal	31	10	3	44
Total	500	200	300	1000

Fig. I shows the ages of patients investigated. 500 cases belong to the first group in which pars vaginalis of uterus was studied. 200 cases (the second group) were investigated at pars cervicalis of the uterus and 300 (the third group) at the urethra. The ages of the women ranged from 19 to 55, and about 95 percent of them were possibly pregnant. Clinical diagnoses of these women are given in Table 1.

In a separate survey, the cervical part of the uterus of two hundred pregnant

women including those with serious trachoma of the eyes examined histopathologically.

Results

Results of the Smear Tests. We have investigated 1000 cases by smear tests and the results obtained are summarized in Table II. The typical Prowazek-Halberstaedter's inclusion body was never found. Sometimes, we found multiform granules resembling the inclusion body in the epithelial cells. However, these granules in the cytoplasma were definitely different from the true inclusion body as judged from our long experience in trachoma study. It is a very important and significant fact that not a single case with typical Prowazek's body was found, and that similar granules instead of Prowazek's body were demonstrated by Poleff's method.

There are so many kinds of organisms in such smears and they outnumber those of conjunctival organisms. The main species of bacteria and Döderlein's bacteria on the basis of relative frequency.

Table 2 Smear test of uro-genital organs.

	Smears of pars vaginalis	Smears of pars cervicalis	Urethra	
			Mucosa	Smegma
Inclusion body	0	0	0	0
Analogous granule	21(4.2%)	9(4.5%)	91(30.3%)	0
Veillonella bacteria	288(57.6%)	95(47.5%)	83(27.6%)	55(55.0%)
Comma bacteria	78(15.6%)	24(12.0%)	80(26.6%)	5(5.0%)
Doederlein bacteria	170(34.0%)	34(17.0%)	85(28.3%)	18(18.0%)
Others		Sperma 7(3,5%)		Spirochaeta 42 (42%)
				Smegma b. 40 (40%)
Total	500(100%)	200(100%)	300(100%)	100 (100%)

Table II represents the frequency of these organisms in the urogenital parts and in smegma. If we had investigated more carefully, the percentage of bacteria in this table would have been greater. It is an interesting finding that several kinds of microorganisms were found at the same time in most cases, but the main species constituted the greater portion of the organisms in number. We therefore presume that there is symbiosis among these organisms, but no relationship between the organisms in the urogenital organs and conjunctival sac.

All attempts to demonstrate inclusion bodies in the scraping materials from the urogenital have failed, nor have we been able to identify any free elementary or initial bodies. The normal bacterial flora of the urogenitals are far more in number than the flora of the human conjunctiva, and we fell that these bacteria as has been previously mentioned were probably normal saprophylic forms. With the special straining technic by Poleff, similar analogous granules in mastcells and mucosa cells (cupcells) are mistaken as pathogenic bodies.

Pathohistological Examinations of Cervical Canals. The histological examinations of the cervical canals were done in 200 biopsy materials. Histologically[11], the cervical epithelium is easily differentiated from that of the corpus in its relation to the subepithelial gland and stroma. The epithelium of the cervix is of two types. The epithelium of the pars vaginalis is similar to the stratified epithelium of the vagina, although the subepithelia; papillae are much less marked. The epithelium of pars cervicalis extends to almost as far as the external orifice, but there are individual variations in its extention.

The epithelium of the endocervix is of an entirely different form. It is of tall cylindrical character (picket cell), much taller than that found in the endometrium, and it normally exhibits no cillia. The nuclei and cytoplasma are different in two epithelia. These differences in the epithelium of the corpus and the cervix are of great practical significance, because upon them is based the histogenic classification of carcinomas. Many former investigators believed that the inclusion body prefers cylindrical epithelium to stratified epithelium.

Table 3 Pathohistological findings of cervical canals

Prowazek's Inclusion body	Diffuse cell infiltration	Follicular form of lymphcells	Mastcell	Trachomatous gland
0	160 (80%	38 (19%)	200 (100%)	7 (7%)

Beneath the mucous membranes of the veering part of pars vaginalis and pars cervicalis a follicular formation and diffuse celluear infiltration were often found, which are called uterus trachomatous tissue figure. These pathological indications have no relationship with Prowazek's inclusion body, and a typical inclusion body was never found in our studies.

As Dr. Poleff[10] points out, his specific staining method is simple, rapid, and yields perfect contrast for inclusion bodies which stain purple with a violet tinge, and their background takes a clear sky-blue color. However, his method may stain the mastcell granules and other intracelluar granules like his trachoma bodies. These cell granules usually increase in the subepithelial tissue in an inflammatory process.

Previously described pictures of trachoma transplanted uterus appear to be non-specific, for diffuse, cellular infiltration in the subepithelial tissue layer which looks like the forms of trachoma follicles and somewhat circumscribed collections of round cells are often seen in non-trachomatous individuals. Among 200 cases we found 160 cases (80%) with cell infiltration and 38 cases (19%) with a follicular form of lymphoid cells, but there was no characteristic findings of trachoma. The gland of the cervix was found frequently to form a retention cyst or so-called trachomagland like structure (7%). The smear test of the urinary sediment and uro-genital epithelium of the mothers whose newborn infants suffered from inclusion conjunctivitis did not disclose Prowazek's body. (See Fig. 2~5)

Fig. 2 Atypical follicular formation and diffuse cellular formation in pars cervicalis uteri. (Case No. 18)×100

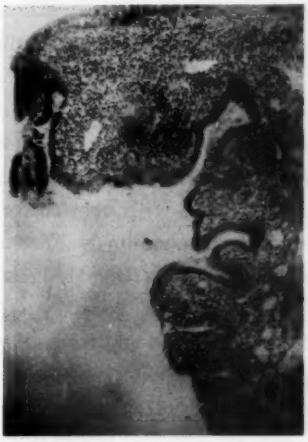


Fig. 3 Circumscribed eollections of roundcells in subepithelial tissue layer. (Case No. 18) ×450

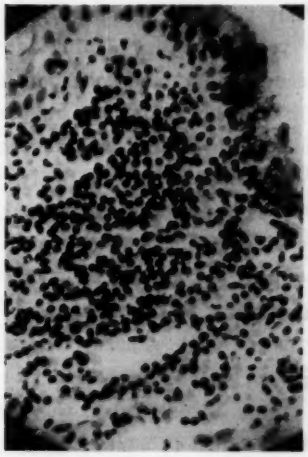


Fig. 4 Diffuse cellular infiltration at boundary of pars cervicalis and pars vaginalis. (Case No. 46)×450

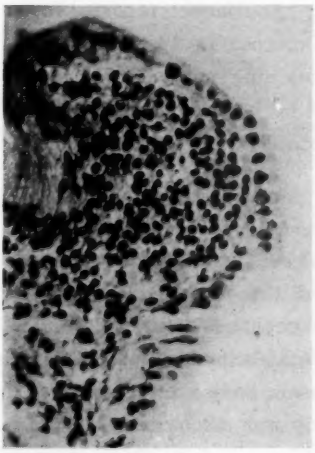
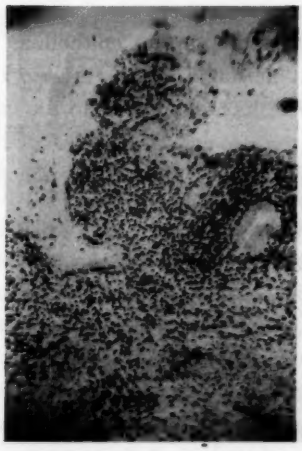


Fig. 5 Diffuse cellular infiltration in subepithelial tissue. (No. 181)×100



Discussion

The results of these investigations seem to problems which need to be discussed:

1) We could not find the inclusions dodies in smear test among one thousand women in the Onoda district where the general incidence of trachoma is estimated to be about 20 percent of the popultation. Therefore, there remains a great doubt

whether the inclusion bodies have a relation to the hotbed of the urogenital trachoma or not. As regards the etiology of inclusion blennorrhea in the new-born, it has been thought by some that the inclusion body causes iafection in the birth canal of the mother, but the authors strongly doubt that the etiologic agent of trachoma is the same as pathogenic urogenital agents. Scarcely any urologists or gynecologists in Japan did ever note such condition due to inclusion body.

2) On the basis of our histological evidence, the inclusion body in the cervical canals of two hundred cases was negative, and the local changes in subepithelial layers were shown not to be specific in trachoma. Because, these round cell infiltrations and pseudofollicles were some times found in subepithelial tissues with cervical erosion.Dr. Okamura et al provided evidence in affirmation of true trachoma, by discussing the relation of the Prowazek's body to the cervical erosion and inferring that the Prowazek's body occurs in the swollen, often infected cervical mucosa rolled out from the cervical ostium. In general, therefore, it appears that these changes of epithelial layers are not specific and bear no relation to pregnancy.

3) In this investigation we used Poleff's staining and other classical methods. However, we failed to confirm the great advantages of Poleff's technic which was supported by recent French workers, for with this method nonspecific granules were easily demonstrated in the mucosa of human body. Formerly, a Japanese author drew attention to the analogous bodies in the trachoma tissue as the possible pathogenic agent of trachoma[14], but we can not accept it now. Abu-Jaubeh reported the occurrence of inclusion bodies in the epithelium of urethral mucosa in 14 percent of trachoma patients at Beirut in 1953. He used Dr. Poleff's staining method for the study, and therefore we have doubts as to his conclusion that he had demonstrated the .inclusion bodies in the uro-genital organs. It is very improbable that the cervical part of the uterus constitutes a hotbed of trachoma[12)13].

Summary

1. The smear test of the scraped epithelial cells was performed on the vaginal and cervical parts of the uterus and urethra of the out-patients at a gynecological clinic in the rural area around Onoda, where trachoma is found in about 20 percent of the population. We could not find a single typical inclusion body, although sometimes an analogous body which looked like the inclusion body was demonstrated in or on the epithelial cells, and the meaning of such a body was discussed.

2. The histological observations with biopsy of cervical canals of 200 cases showed no specific characteristics of trachoma or inclusion body in epithelium.

3. The Poleff's contrast staining of trachoma body which was used by Abu-Jaubeh in his urogenital trachoma study at Beirut has proved unsuitable for this purpose, for with this technic, granules of mastcells and of other origin can not be differentiated from the inclusion body.

Therefore, we could not establish any definite evidence of feminine urogenital disease caused by Prowazek's inclusion body.

(Published in Acta O. Jap.)

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THE AQUEOUS OUTFLOW

Kohei OHASHI

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Introduction

All too frequently the ophthalmologist finds himself at a loss for obvious explanation of ocular tension elevation in glaucoma. Various attempts have been made to determine the aqueous outflow more accurately or to confirm their presence.

For the purpose of the advisable examination in glaucoma, especially to determine the aqueous outflow, the dropping rate of ocular tension by bulbar compression test (D%), the repairing rate to the primary ocular tension (R%) and the outflow resistance (W) were measured by the author's bulbar compression test as a simple loading test and a double loading test with drugs in a number of normal and glaucomatous eyes. Regarding the procedure, bulbar compression was applied continually to the globe for ten minutes at fifty grams constantly.

Furthermore, in the author's generalized blood pressure measurement with this bulbar compression test, the anterior ciliary venous pressure (CV) and vortices venous pressure (VV) were measured by the author's newly revised Bailliart's method which has been already reported (1951). Thereafter the anterior outflow ratio CV% and the posterior outflow ratio VV% were calculated in the normal and glaucomatous eye, without, or with some autonomic nerve drug loading with the experimentary outflow measurement in the rabbit's eye with the same bulbar compression test.

Thus the author has found that the aqueous outflow rate calculated by the author's

technique probably accounts for tde characteristic feature of aqueous outlets in glaucoma.

Dropping rate, Repairing rate and outflow resistance. Dropping rate D% of the ocular tension just after the bulbar compression has been removed using a Bailliart's ophthalmodynamometer was calculated respectively by the following formula:

$$D\% = \frac{P_0 - P_1}{P_0} \cdot 100$$

Repairing rate R% which shows nearly the returning grade of the falling ocular tension to the primary tension to the primary tension 30 minutes after compression was removed, was calculated by the following formula: $R\% = \frac{P_2 - P_1}{P_0 - P_1} .100$

And the outflow resistance W can be expressed by the following formula:

$$W = \frac{31}{P_0 - P_1} - 1$$

In here P_0, P_1 and P_2 stands for the primary tension, tension just after removed compression, and tension 30 minutes later.

The mean pressure of brachial blood pressure BP M was calculated by the following formula: $BP\ M = \frac{\text{Pulse Pressure}}{3} + \text{Minimum Pressure}$

The results of the author's compression test and its outflow rates and W in the normal 170 eyes were divided into 5 age groups with the average values as shown in Table 1.

Table 1 Normal Simple Test

Group	Number	Age	D%	R%	W	M BP
I	33	15~19	76.6	96.6	1.14	80.35
II	39	20~29	73.0	96.7	1.28	85.40
III	37	30~39	71.8	95.0	1.41	87.92
IV	32	40~49	68.8	96.3	1.61	92.57
V	29	50~70	66.6	93.8	1.69	94.65
	Total Average 170 eyes		72.9 ±3.31	95.8 ±3.55	1.48 ±0.44	88.17 ±5.25

As shown in this table, we find the normal D% indicates within 66.6 to 76.6%, having a conspicuous tendency to decrease D% in the senile person. On the contrary the outflow resistance W increases, depending upon the increasing of age, resembling the senile change or angiosclerosis in the ocular tissue. Therefore, the tendency of the increasing resistance W in the senile rather than the young person was evident as showing a significant reciprocal proportion between D% and W. The value of the normal W showed 1.14-1.69, and 1.48 in average. But no definite relationship between ocular tension and blood pressure was recognized in the normal eye.

As the relation between aqueous outflow and diurnal variation of the value of W, while the normal ocular tension and the variation of W are showing an apparent relativity, the glaucomatous behavior differs. Especially in the congestive glaucoma, the diurnal variations of W behave in a desultory way with ocular tension, resembling

an essential difference between the simple and congestive type of glaucoma.

The relation between aqueous outflow and ophthalmic rigidity was also examined in the author's compression test. Under the state just after the compression the ocular rigidity was also measured by Friedenwald's method in 20 normal eyes with and without drug loading, such as cocaine, adrenaline, neosynesine, pilocarpine, imidaline, 3% saline solution and contomine (chlorpromazine).

From these results of the fluctuations of ocular tension and ocular rigidity, the author presumed that, the outflow resistance W might be dependent upon the ocular rigidity in the normal eye. It seems under the state of bulbar compression, the increase of ocular rigidity which is due to the decrease of elasticity of intraocular tissue, may lead to the rise of resistaece W, which is depending on the intraocular vessel contraction and change of tension.

Furthermore the rigidity of the central retinal artery and W were compared in the author's compression test in 60 normal eyes, divided into 6 groups as 10, 20, 30, 40, 50, 60 years of age. In this compression test, the imidaline injection test was added.

According to the imidaline injection test, first the ocular tension, retinal blood pressure and rigidity are measured, and 20 minutes after injection of 1 cc imidaline or priscol a 50 gm. compression is added to the eye for 10 miuntes. Then just after removal of compression, measurement was again made, resistance W was calculated. These, the author's simple compression tests and imidaline injection tests were performed also in 46 cases of hyperpiesia, as Keith-Wagner group 1-14, group II-18, group III-10, group IV-4 eyes.

On the other hand, the rigidity of the temporal iridic artery (posterior long ciliary artery), by using diaphanoscope combined with a Bailliart dynamometer, was measured in the same way as with the bulbar compression test.

Therefore, fluctuations of the retinal and choroidal vessel rigidity under the state of bulbar compression were compared with the author's D,R,W etc.

It is thus concluded that the aqueous resistance W is dependent upon the intraocular vessel rigidities and apparently shows an inverse relation to the dropping rate D but is not influenced by either ocular tension or Friedenwald's rigidity in normal eyes.

Aqueous cutflow ratios. The anterior aqueous outflow ratio (CV%) was calculated as follows: $CV\% = \frac{CV\text{-}OT}{OT} \cdot 100$

In this formula, CV indicates the anterior ciliary venous blood pressure, OT indicates the ocular tension.

The posterior aqueous outflow ratio (VV%) was calculated as follows, as VV indicates the vortices venous pressure: $\frac{VV\text{-}OT}{OT} \cdot 100$

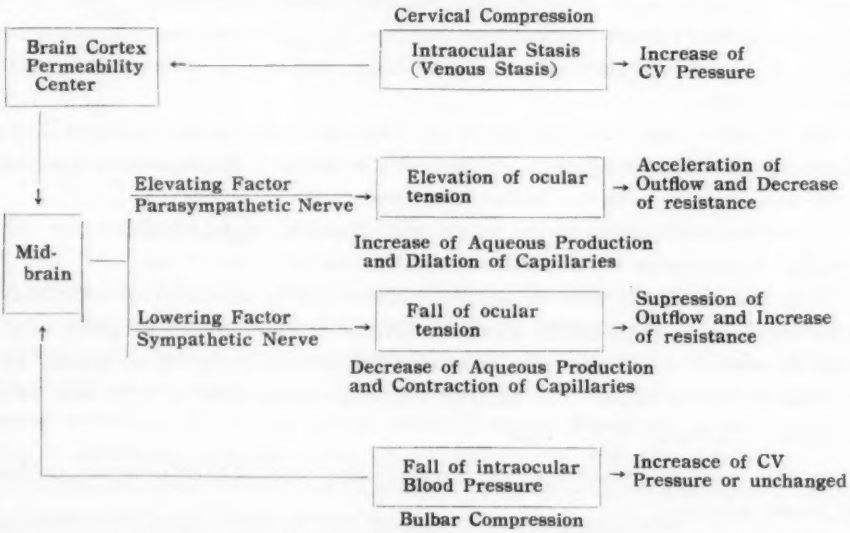
(These CV% and VV% have been reported previously by the authors in the paper of Jikei-kai Medical Journal Vol. 1, No. 1, 1954, in Japan)

When comparing the average value of primary intraocular blood pressure in normal human eyes with those of D,R,CV%, VV%, W, the data as described in Table 2 can be obtained. As shown in this table, the ocular tension there showed as (OT) 17.2 mmHg., Anterior ciliary arterial pressure (CA) maximum 73.8 mmH., minimum 42.2 mmHg., Anterior ciliary venous pressure (CV) 9.2 mmHg., Central retinal venous pressure (RV) 21.8 mmHg., Vortices venous pressure (VV) 22.2 mmHg., Central retinal arterial pressure (RA) maximum 70.6 mmHg., minimum 42.2 mmHg., Brachial blood pressure (BP) maximum 129.8, minimum 80.4 mmHg. in the primary pressures. Furthermore D 68.7%, R 97.8%, CV% 63.8%, VV% 116.2% and W 1.52 was seen in average just after compression removed. Therefore we can find that these of D,R,W in the normal eye nearly coincided to that in Table 1.

Table 2 Normal Blood Pressure and Outflow (mmHg., 30 eyes)

OT	RV	VV	CV	CA	RA	BP	R%	D%	CV%	VV%	W
17.2	21.8	22.2	9.2	73.8-44.8	70.6-42.4	129.8-80.4	97.8	68.7	63.8	116.2	1.52

Schema of Tensian Control


Cervical Compression
Brain Cortex Permeability Center
Intraocular Stasis (Venous Stasis)
Increase of CV Pressure
Elevating Factor
Parasympathetic Nerve
Elevation of ocular tension
Acceleration of Outflow and Decrease of resistance
Mid-brain
Increase of Aqueous Production and Dilation of Capillaries
Lowering Factor
Sympathetic Nerve
Fall of ocular tension
Supression of Outflow and Increase of resistance
Decrease of Aqueous Production and Contraction of Capillaries
Fall of intraocular Blood Pressure
Increasce of CV Pressure or unchanged
Bulbar Compression

Furthemore the measurements of D,R,W in the compression test were made in normal eyes 20 minutes after injection of imidaline, contomine, saline solution, pilocarpine, atropine, finaline, adrenaline and neosynesine, and the CV%, VV% was calculated in the normal and glaucomatous eyes. Thus comparing with the series of these data,

the author reached the following conclusion.

In general, viewing the results of the glaucomatous eye, while I found the distinct decrease of D and R, the apparent increase of W, the anterior outflow ratio CV% in primary tension always inclined to increase more towards the negative side than that of the normal eye. Therefore the expression of this negative increase of CV% may be probably induced by the state of an increasing W which is possibly in alignement with the fact, that Goldman's false outflow pressure, which accelerstes in glaucoma,is evident.

The decrease of posterior outflow ratio VV% was also found in glaucoma. Therefore it reveals plainly that the glaucomatous posterior outlets, which mainly exist in choroidal veins, may show an apparent disturbance of the function as an important posterior passage. However in the fall Po-CV pressure there was no correlative evidence between the fall and W in 65 cases of simple glaucoma.

Although in these 65 cases of simple glaucoma, I found, such interesting evidence. Accordingly a sinificant correlation was apparently found between D and CV%, D and VV%. or between CV% and VV%, and these correlation coefficients were 0.63, 0.88 and 0.37. But the correlation coefficients between R and VV%, R and D,R and CV% or R and W were negligibly reduced. Also in the relation between age and D, age and W, age and CV%, age and VV%, there were no significant relations.

Through these facts one may interpret this to be an evident phenomenon, that the glaucomatous D,W distinctly differs from that of the normal condition.

Recently Henderson (1910), Weinstein (1953) have stated that the main change of the lowered outflow may be due to the senile change or angiosclerotic alternation in outlets. While the problem of the existence of angiosclerotic changes in glaucoma-development has been an interesting problem in our field, it is still considered disputable.

With regard to this problem, however, the author would oppose from his standpoint, on account of the above mentioned difference of D, W in glaucoma. In our data, there was also no significant correlation between the iridic arterial rigidity and D or W in glaucoma, while it even showed a significant value in the normal eye.

When comparing the results of the compression test of the glaucomatous eye after receiving injection of imidaline with the normal control, the former demonstrated an apparent change, as the decrease of D, the increase of W. On the contrary, in the contomine injection test, a strong fall of tension was produced as the increase of D, the decrease of W.

These facts reveal the evident response with autonomic nerve drugs in glaucoma. It is therefore of importance to know, whether the control mechanism exerts itself mainly as in a central or peripheral action.

Therefore, the author carried out further, the neck compression test, and head lowering test with the measurement of D and W.

In the author's neck compression test and head lowering test with and without drug loading of imidaline injection, it can be understood that the following facts may

be concluded:

When the artificial temporary rise of ocular tension occurs by the producing of the ocular tension elevating factor, due to the uveal venous stasis, D should be accelerated immediately, and the passive opening of the aqueous outlets may also occur at the same time.

Furthermore in these tests, the author ascertained the evident facts, that in the imidaline injection test the production of the ocular tension elevating factor might be accelerated, but in the chlorpromazine injection test that might be inhibitted.

Mechanism of the aqueous ouuflow. From the results above mentioned, the author assumes tee mechanism of the aqueous outflow as shown in this Schema.

When imidaline is injected, the entire periphery of the sympathetic nerve becomes blocked, the intraocular capillaries dilated, the permeability accelerated and the ocular tension elevated. On the other hand, when chlorpromazine is injected, the central sympathetic nerve especially the fibers betweenn midbrain and brain cortex become blocked, the permeability suppressed and the ocular tension lowered with the passive contraction of capillaries.

In other words, the artificial uveal stasis caused by the injection of imidaline, 3% saline solution, same as by the cervical compression test or head lowering test, may accelerate the production of the tension elevating factor from the diencephalon, acting reflectively as the cholinergic or parasympathetic stimulation pass through the sympathetic fibers intermingled in the trigeminus and oculomotor nerve.

Although, when the temporary fall of ocular tension is produced by such a bulbar compsession test, and fall of intraocular blood pressure or the results of chlorpromazine injection, the ocular tension lowering factor may be produced from the diencephalon,acting reflectively as the suppression of the permeability and contraction of the capillaries, the decrease of the aqueous formation and outflow, and the increase of the outflow resistance.

According to these author's experimental studies it is presumable that, on one hand, aqueous formation is accelerated and on the other hand, the outlet becomes enlarged. Not only Schlemm's canal and collector but also the intrascleral plexus and vortices vein become enlarged and adjust the ocular tension.

Therefore the autheor is of the opinion that, is is presumed that the hypersensitive condition of the paraspmpathetic nerve is the cause of glaucoma. Although various mechanisms can be considered in the maintenance of ocular tension, there should be always a balance between the outflow and production, and if dilation of intraocular vessels should occur, both the outflow and production should become accelerated.

This balance is controlled by the ability of self-control, and if this is hindered an uveal stasis occurs and the ocular tension continues to hold its tendency of elevation.

Glaucoma may be based upon the rise of the outflow resistance which is mainly due to the disfunction of trabeculae and the unbalance of the central controlling ability, which should be expressed from the midbrain and the brain cortex.

Summary

The author reported the measurement of the dropping rate D, repairing rate R, outflow resistance W and anterior outflow ratio CV%, posterior outflow ratio VV% in normal rnd glaucomatous eyes, and further discussed the variant of D,R,W,CV%, VV% or intraocular blood pressure and rigidity in the bulbar compression test, comparing with some autonomic nerve drug loading.

According to the author's conclusion, the entity of the self-control mechanism of ocular tension should be due to the balance between the ocular tension elevating and lowering factor, which may be produced from midbrain, under the conducting action of the brain cortex.

When the artificial uveal stasis is caused by drug injection or the cervical compression and head lowering loading test, the production of the tension elevating factors may be promoted, as if the tensional sensitive sympathetic nerve, which intermingled with the trigeminus, oculomotor nerve, is stimulated, so that the ciliary capillaries may dilate and the permeability may accelerated the rise of tension.

On the other hand, when the temporary fall of ocular tension will occur by such a bulbar compression test, and fall with intraocular blood pressure, or the state of chlorpromazine injection, the ocular tension lowering factor may be produced and inhibit the permeability, thereafter both, the aqueous formation and outflow and the resistance would be decreased.

In general in the bulbar compressed stage, the tension lowering factor which reflectively producted would exert itself towards the vessel contraction and if the bulbus is strongly compressed, the passive opening of outlets will occur. Though after the removal of compression, the the tension elevating factor would be produced immediately, then the vessel dilation and opening of outlets occur; not only Schlemm's canal and collectors but also the intrascleral venous plexus and vortices vein become enlarged and adjust the ocular tension. There exists the steady tonus of both the tension regulating factors in the normal eye.

Furthermore the outflow resistance is depending upon the senile change in the ocular tissue, closely related to the function of trabeculum in the normal eye, but the glaucomatous resistance always differs, showing no relation with the senile change or angiosclerosis.

Therefore the author is of the opinion that, it is presumed that the hypersensitive condition of the parasympathetic nerve is the cause of glaucoma.

Glaucoma may be based upon the rise of outflow resistance, maily due to the disfunction of trabeculum and the unbalance of the central controlling ability.

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OBSERVATION OF THE OPENING OF NASOLACRIMAL DUCT (REPORT II)

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Introduction

The diseases of lacrimal duct, which are encountered so frequently in our daily clinic, have hitherto been rather kept at some distance by both oculists and rhinologists because the lacrimal duct is situated at the borderline inter ophthalmology and rhinology. In general, the oculists have treated the obliterated ducts customarily conservatively, strictly speaking, without any anatomical self-confidence upon their healings. For example we oculists perform so frexuently the probing with bougie, but we act so at random without making sure whether the bougie gets through the adequate way or not. Therefore the accurate observation upon the terminal portion of the nasolacrimal duct should be indispensable for the study of physiological and pathological conditions of the lacrimal duct.

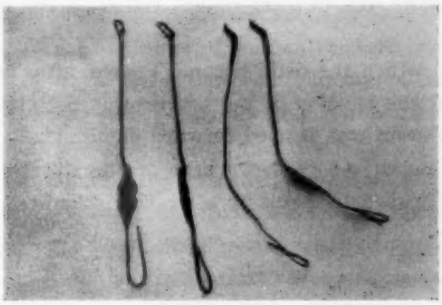
Formerly, Sakaguchi (1910), Schaeffer (1912), Masugi (1914), Ashikaga (1925), Iwata (1927), Tanaka (1935) and others studied about the morphology of the lacrimal duct or ostia nasolacrimalis, but all these studies dealt with dead materials. Of course radiographical studies of the lacrimal duct were carried out in a living human body by Nakamura (1928), Totsuka (1954) and others, but this method is too transient to observe the duct and ostium sufficiently.

I devised a new mirror to observe the nasolacrimal ostia and experimented with this instrument during three years upon many normal and pathological cases with good results. Such an idea seems to be quite simple but no one has hitherto realized this idea.

Instrument and Method

I designed a kind of reflecting mirror named nasolacrimaloscope to observe the terminal portion of nasolacrimal duct. This instrument consists of a trapezoid mirror, 3.5m.m.×7.0m.m (or 3.0m.m×6.0m.m.), and a flexible silver handle, to which the ordinary Bowman's bougie is applicable. (Fig. 1) After anesthetizing the nasal mucosa this mirror is easily inserted into the nasal cavity and then the reflecting image on the mirror is observed with the head mirror of the rhinologist, projecting the light into the nasal cavity simultaneously. This procedure is very simple but requires some skill and experience.

Fig. 1 Nasolacrimaloscope (applied Bowman's bougie)



The routine method of observation is as follows.

1). It is convenient to lay the patient on his back.

2). Apply 0.1% epirenamine and 3% cocaine to the nasal mucosa sufficiently until the mucosa reflex becomes absent.

3). Observe the ostium inserting the nasolacrimaloscope.

4). Observe the changes of ostium during the blinking.

5). Observe the changes after washing the duct with saline solution or after instillation of fluoresceine.

6). Observe the changes during inserting a bougie from the conjunctiva.

7). Observe the changes inserting the bougie bended right angle into the ostium from the nasal cavity.

Materials and Results

One hundred and twenty persons aged from 8 to 78 were examined, of whom both sides of 40 persons were observed and the single sides of 80 persons. Totally 160 cases were observed but in 27 cases among them the ostia were invisible owing to the narrowness of the nasal cavity or hypertrophy of nasal conchae. One hundred and thirty three visible cases were classified pathologically: normal 70 cases (among them

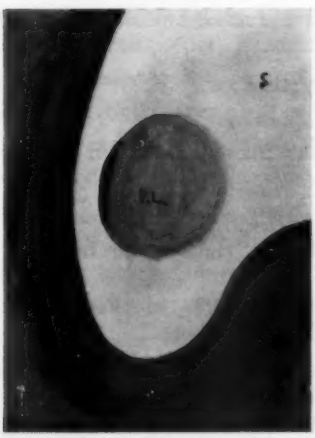
9 cases of stridor nasolacrimalis), stricture of nasolacrimal duct 27 cases, obliteration 26 cases, chronic dacryocystitis 8 cases and I postoperative case.

According to my observations the form of ostia are to be classified in three types.

Type I. 66 cases in which the ostia were always opened and visible. The ostia had the forms round or oval and their sizes were presummably 3~4m.m. because their images were almost equal to the width of the mirror. The margin of the ostia was sharp in the side of concha, but in the opposite side it may show a sharp edge or gradual concavity. The so-called Hasner's valve showed various forms covering the ostia partially or totally. In 9 cases of stridor nasolacrimalis the ostia were almost opened and the Hasner's valves were developed rudimentally. After instillation of fluoresceine or washing the duct, the movewents of the valve became distinctly observable,namely with the act of lid-opening the content of the duct was pushed foward into the nasal cavity and with the act of lid-closure the content was aspirated. The mucosa inside of the duct was to some extent visible in the cases in which the ostia were opened. (Fig. 2)

Type II. 6 cases ih which the ostia became visible after washing the duct with saline solution. At first the location of the ostium was not clear, but after the irrigation of the duct, the solution was pushed forward rhythmically in correspondence with the blinking, from the end of tne groove, where presumably the ostia existed. Sometimes the ostia became opened triangularly after the irrigation. (Fig. 3)

Fig. 2 Normal ostium, type I.
U.M. inferior nasal concha
M. mucosa of nasolacrimal duct
S. nasalmucosa



Type III. 61 cases in which the ostia were not detectable despite of irrigation or instillation of fluoresceine. Among these some cases showed a diffuse outflow of fluoresceine presumably from the narrow ostia covered by the valve. In these cases the probing with Bowman's bougie could not show the location of the ostia, because the bougie generally appeard penetrating the mucosa in an unexpected situation.

Discussion

Tanaka reported in the examination of dead materials that the forms of the nasolacrimal ostia were groovy, slitlike, oval and round. But 1 found in the living bodies almost always a round or oval ostia presummably because the groovy or slitlike ostia were covered by the Hasner's valve. About the function of Hasner's valve

Fig. 3 Movement of Hasner's valve(P.L.)

A.	B.	C.
Normal state	The valve is closed by negative pressure of duct	The valve is opened when the lacrimal sac is pressed

Tanaka said that, in 7 cases out of 99, the valve seemed to have no use. According to my observation the forms and sizes of this valve were extremely various and the function was considered to prevent the back flowing of nasal secretion or air into the duct, because all the cases of nasolacrimal stridor showed a round or oval ostia with rudimental valves.

The influence of the blinking movement upon the outflow of the tear has been a problem of controversy. Nagashima studied with his special apparat and concluded that by the act of lidclosure there shoud occur negative pressure in the tear sac. I observed that the content of the nasolacrimal duct was aspirated during the act of lidclosure and flowed out by the act of lidopening. Namely, the mechanism of the tear outflow is considered that at first the tear in the conjunctiva is aspirated by the negative pressure of the tear sac produced by the act of lidclosure and then the tear in the sac is gradually pushed forward by the elastic pressure of that sac, duct, and neighbouring tissues.

Summary

I observed 160 cases of normal and abnormal terminals of nasolacrimal duct, making use of a new self-designed nasolacrimalscope. In 27 cases out of 160 the observation of the ostia did not succeed, chiefly, because their nasal cavities were too narrow to insert the mirror. But in 133 cases the observations and experiments were carried out successfully. The forms of ostia were classified in three types. The forms and sizes of Hasner's valve were extremely various and its function was observed. To observe the nasolacrimal ostia accurately it is very useful to examine the physiological state of tear outflow as well as to make sure of the conservative treatments for obliteration such as probing or vinyl tubing.

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MORPHOLOGICAL STUDIES OF THE PIGMENT GRANULES OF RETINA BY THE ELECTRON MICROSCOPE

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In 1951 M.Sebruyns, by observing the pigment granules of the retina of an ox eye by means of the electron microscope, discovered that at one of the extremities of each granule there existed a filamentous process, and reported that by the expansion and contraction of these processes were caused the emigration of the pigment granules. This study attracted public attention at that time as a very interesting one, and Kinugasa (1953), R.Binder (1953), M.Rabaey (1953) etc. tried one after another to find out these processes but with no results. Until now their existence has still remained doubtful.

Recently I examined the pigment granules of a human eye by means of the electron microscope, and was able to find the same pigment granules with a kind of filaments on them as M.Sebruyns described. Adding to this, I got some new discoveries, such as the detailed structure of this filament and the way of its being attached to the granule. Here I am going to report my examinations.

Technique

I used, as the sample material of the experiment, an eye taken from a human body within 12 hours after death. The eyeball is sectioned in two through the equatorial plate. The vitreous body and the retina are carefully removed with a pincette and a fude (Japanese brush for writing). Next, by lightly scratching the layer of the pigmentary epithelium with a spatula, one can get plenty of pigmentary cells, which are made to float on a hypotonic solution of chloride in a watch glass, and left still. Several hours later, the cells begin to swell and are destroyed; then, out come the pigment granules, and lie at the bottom of the glass. The upper layer is cast aside and the pigment granules are collected, which are removed into a test tube which is filled with

a physiological solution of sodium chloride, and are shaken vigorously in it, until the solution is made uniform, as seen with the naked eye. This solution is taken into an injector, is dropped on a mesh covered with collodium, and dried. By drying, however, is educed crystallized salt which prevents examining by the microscope. In order to eliminate this salt, I dropped some distilled water on the dried mesh and dissolved this crystal of salt, which I sucked up with an injector, drying the remainder again. This was the sample material to be examined by the microscope.

The other method: By directly floating the gathered cells of pigmentary epithelium on distilled water, I let the pigment granules come out of it. Those also were made to be sample material for the examination.

Accelerating voltage of the electron microscope was 100K.V. and 150K.V., The material was studied with a direct magnification of 3000 to 5000 times.

Result

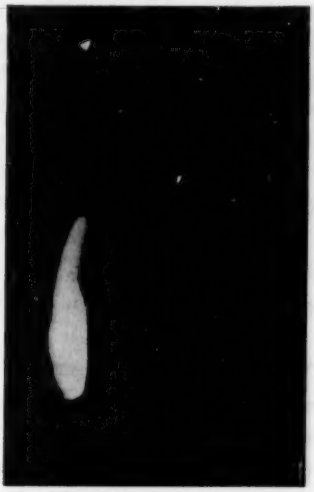
The pigment granules are vary polymorphous as showh in the figure 1. They can be roughly classified in two, the oval and the globular. The oval granule is 2 to 3μ in diameter, and the globular one 1μ. The surface of the granule is not smooth, but has many irregular tiny projections. Neither the oval granule nor the globular one is passed through by the electron beam, so a contrasting picture can be made of it. But when the examination is made with accelerating voltage of 150K.V., a faintly shaded part on an edge of a small granule is, at times, observed; may be this part has exceptionally been passed through by the electron beam. This shade, however, is balanced

Fig. 1 The pigment granule of the retina. Cr-shadowing. ×7.000

Fig. 2 The filamentous process of the pigment granule of the retina. Cr-Shadowing. ×10.000

Fig. 3 It is clear how the filament, separating in two, is attached to the granula. Cr-shadowing. ×10.000

Fig. 4 The filament is separated in two at the ends. Cr-shadowing. ×10.000



in density, and no structural mechanism seems to exist inside the granule. Sometimes some thin filamentous processes are found running irregularly between the granules. But I could not get any pictures where the filaments semed to be surely attached to any of the granules. The impression above is got from the sample material of cells of pigmentary epithelium dealt with distilled water. While in the sample material of cells of pigmentary epithelium managed with hypotonic solution of sodium chloride, can be found a granule which has a thin filamentous process on one of its extremities, as is shown in figure 2,3 and 4. And it is only the oval granules that have these filaments, no globular ones are having these filaments.

This filament has oblique striae on it. It is a spiral which looks like a piece of twisted rope. The width of most of the filaments is from 50 to 75mμ; that of some of them reaches 100mμ. Near granules these filaments become very thin, the width being from 35 to 50mμ. At the part where it is attached to the granule, the filament appears flat, taking the form of a tiny fan, and the contrast of the picture is weakened (Fig. 2). One of the pictures shows that the filament is divided in two thinner ones, and the way how they are connceted to the grenule is clearly observed (Fig. 3). Another picture shows that the other end of the filament is often separated in two thinner ones (Fig. 4), another figure showing these thinner ones only. Another shows that such filaments as said above sometimes branch out half way, the end of each of them being attached to the granules. As was said above in "Technique", in order to remove salt cristal I repeated several times the operation of dropping distilled water on the mesh and of sucking it up, in the last step of getting the sample material. The sample material thus obtained is free from any impurities, and is better examined than otherwise, but at

the same time it is difficult to find the granules to which the filaments are securely attached.

Discussion

Of the studies of the pigment granules of the retina by the electron microscope, M.Sebruyns' about an ox eye is the first, and those of Kinugasa, R.Binder and E.Orth, M.Rabaey et G.Vandermeerssche etc. followed it.

M.Sebruyns made chloramine act on the pigment granules of the retina, and the result of it was that each granule split into a kind of a membranous sac and numerous tiny granules. From this fact, he concluded that a granule consisted of tinier ones contained in a membrane like a sac. R.Binder etc. agree with M.Sebruyns on the points that on the surface of the oval granule there exist as many tiny irregular projections as to suggest some inner structural mechanism, and that near the edge of the globular granule is seen a tinier globular body about the size of 50mμ. M.Rabaey etc., however, oppose them, saying, it is true that the surfrce of the granule is rugged and uneven, and has the tendency to be easily destroyed by chloramine, but it has no inner structural mechanism in it.

I examined the granule with accelerating voltage of 150K.V., and the result was that on an edge of the granule through which some electron beam seemed to have passed, there appeared a part that was faintly shaded. The shade, however, was balanced in density, and there existed no such tiny granules as had been mentioned by R.Binder; I got no such impression as to suggest any inner structural mechanism.

Next, in the sample material of the granules which have been dealt with distilled water only, some filaments are sometimes found lying irregularly between the granules but none of them are surely connected to the granules. On the contrary, in every sample material of pigmentary cells which has been dealt with a solution of sodium chloride, can be found granules at one of whose extremities filaments are fastened. It is M.Sebruyns who first reported that there existed these filaments, attached to the pigment granules of the retina. He examined the pigment granules of the retina of an ox eye and described that each granule had a process like a filament at one of its extremities, that it was 4 to 8 times longer than the granule, that the width of it was various, that it had oblique, spiral striae, and that the expansion and contraction of it caused the emigration of the pigments of the retina. Later, however, Kinugasa, who studied with an ox eye after M.Sebruyns, reported that there existed no such process. Okuda added to it the same result as Kinugasa. R.Binder, too, conducted the experiment with a human eye and stated that such a process like a filament, as had been mentioned by M.Sebruyns did not seem exist. M.Rabaey, too, tried in vain to find this process in the eyes of a human, a mammal, an amphibian, a fish etc.. Thus, up to the present, all have denied the existence of the process like a filament on the pigment granule of the retina, except M.Sebruyns. Now, in my experiment, at the last

step of making the sample material, I wash the mesh twice or thrice with distilled water in order to remove the crystallized salt on the sample. After the washing is repeated many times, the finding of granules, to which filaments are surely attached, will be very difficult, even in the sample which has till then been dealt with under the same conditions as above; that is, filaments and granules are easily separated by washing only. It may be said that the connection is very unstable. Therefore, the conflicting results of the students above are perhaps caused simply by the difference of the way of producing the sample material.

This filament is as wide as 50 to 100mμ. and is generally three times the length of the granule. The filament has oblique, spiral striae, which corresponds to the Sebruyn's report. I found, further more, in my experiment, that this filament was divided into two thinner ones at the end where it was attached to the granule, and that the other end of it was often seperated into two parallel ones. The above fact seems to show that the filament is actually a double helix formed by two thinner ones, not one single filament twisted spiral. Now, Sebruyns reported that the emigration of the pigments of the retina was caused by the expansion and contraction of these processes like filaments. It has been known that the pigment granules of the retina, when the retina is in light adaptation, emigrate toward external prexiform, and, when it is in dark adaptation, they, which have been emigrating till then, gather together at the bases of the cells of pigmentary epithelium. It has also been known that this phenomenon is caused not only by light but also by various physical or chemical stimuli, these being no less effective than light. The achievements on this line are too many to be mentioned. However, in spite of a lot of discussions from of old, the question as to what gives histologically the impetus to the emigration of the pigment granules, has not yet been settled. Up to now it has been believed that cells of pigmentary epithelium have, on the side where visual cells exist, a lot of projections of protoplasms, which cut inamong cones and rods. Heidenhein states that these projections are, though very delicate, fixed among visual cells, and that the emigration of the pigment granules is caused by the vibration of the protoplasms which form these projections, Verne states that the projections of pigmentary epithelium look like amoebae, and when they expand and contract like the pseudopodia of amoebae, the emigration of the granules is caused. Spaeth describes that cells of the pigmentary epithelium have the power to contract as a smooth muscle. Thus, there have been many discussions about the emigration of the pigments, and yet none of them is decisive. These conflicting views have been caused, I think, by the obscurity of the construction of pigmentary epithelium, especially, by that of how cells of pigmentary epithelium and visual cells are correlated to one another, as well as by the uncertainty whether the granules themselves are movable or not. Lately Uyama turned his attention to this relativity between cells of pigmentary epithelium and visual cells. He carefully cut the retina of the eye of a human or a monkey into horizontal slices, ranging from pigmentary epithelium to visual cells, and studied

them section after section successively until the relativity had been clarified. His study made it clear that on the side of cells of the pigmentary epithelium, where visual cells were attached, there existed no such protoplasm projections like filments as had been acknowledged by other research-workers were actually a very thin and long cylinder like sack produced by the extensions of the boundary membranes of the cells, which presented the appearance of pseudopodia of amoebae. The tip of the cylinder tapered off until it had grown into the tunic of the inner member of a coned visual cell inside the cylinder, and farther attained, going with the tunic, to the external prexiform, to relate it. Yamamoto, too, states that the eye of a cat, a hen or a frog has the same construction as above. Thus, the projection of pigmentary epithelium of the retina is neither a cilium nor a string of protoplasm as has been acknowledged, but the elongation of the cell body itself, the tip of it growing into the tunic of the member of a visual cell until it is combined with the external prexiform; it clearly presents the appearance of being fixed. So it is impossible that the projections should expand and contract freely like the pseudopodia of amoebae. The emigration of pigments is not caused by the granules, which have been believed by many to be moved secondarily by the expansion and contraction of the projection of pigmentary epithelium, but must be caused by the granules themselves which move freely within the projections of the epithelium.

Now, the filament of the pigment granules is, as I have observed above, a double spiral composed of two thinner ones. Here is the mechanism very favorable to make one of expansion or contraction. Besides, in the neighborhood of the nucleus at the base of the cell, there exist chiefly globular pigment granules, and in the projections pin-shaped ones, by which, it has been believed, the pigment emigration is caused. In my experiment, I found that the granules which had filaments were all oval, and that globular ones had no filaments. From these facts, it goes without saying that the filaments mentioned above are closely related to the migration of the pigment granules of the retina. Only, it is a pity that my experiment can not comfirm this fact because the observation is conducted outside the cell, and yet it is not hard to suppose that when the spiral of the filament is loosened, the granules will emigrate toward the external prexiform, and when tightened, they will gather together at the base of the cell; that is, it is the expansion and contraction of the filaments that the migration of the pigments of the retina is caused, as was stated by M. Sebruyns.

Conclusion

From the observations, by the electron microscope, of the pigment granules of the retina of a human eye, I have got such conclusions as follows:-

1. The pigment granules of the retina are polymorphous.
2. Even when the accelerating voltage of the electron microscope was raised to 150K.V., no impression which suggested any inner constructural mechanism of the

granules, was obtained.

3. In the retina of a human eye, too, there exist the pigment granules which have processes like filaments, as were observed by M.Sebruyns. This filamentous process is 50 to 100mμ wide, and is a double spiral composed of two filaments. So M.Sebruyn's doctorine that the emigration of the pigments of the retina is caused by the expansion and contraction of these filaments is, I think, proper.

Now, laying down my pen, 1 must express my hearftul thanks to my respected teacher, professor Fujiyama for his kind guidance.

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HISTOPATHOLOGLCAL STUDY ON THE ANENCEPHALIC EYES
REPORT I. HISTOPATHOLOGICAL FINDING OF RETROLENTAL FIBROPLASIA IN THE ANENCEPHALIC EYES.

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There are two theories, the prenatal and postnatal, with respect to the pathogenesis of Retrolental Fibroplasia which are still ununified. The men who consider it as of a postnatal origin, mention that clinical and histological there are no findings in the eyes of premature infants immediately after the birth, the high incidence in the oxygen inhaled premature infants. Recently there are many who consider as the cause of oxygen, from the experimental works of producing similar changes, to that of retrolental fibroplasia in humans by letting young animals inhale highly concentrated oxygen, thus giving an impression of postnatal origin. With respect to this program, Yoshioka[27] has concluded previously that the retrolental fibroplasia is of a prenatal origin from noticing the early pathological change of the disease in the eyes of premature infants who died soon after birth. However to make this conclusion at the present situation when the role of oxygen is thought to be important, it is necessary to obtain stillborn infants as material rather than premature infants which had inspired air even for a short time. For this purpose 30 eyes of 15 stillbirths anencephalus were obtained for histological study to conclude the pathogenesis of the disease whether it is of a prenatal or postnatal origin.

Materials and Methods

The materials were obtained from 15 anencephalus infants collected by the Departmet

of Pathology (Director: I. HAYASHI) of Nagasaki University from the district of Nagasaki

The eyes were extirpated from the formalin fixed corpse, imbedded in celloidine, serially sectioned and stained in hematoxyline-eosine, van Gieson's, Bielschowsky's Kultschitzky's and Nissl's staining.

Results

The main clinical and autopsy findings of the 15 anencephalic fetuses are shown in Table 1. Among this anencephalic fetuses 2 cases of retrolental fibroplasia were noticed. Their pathohistological findings are mentioned in the following.

Pathohistological findings of the eyes. Case 5. Left eye: The size of the eyeball was 17.2×16.7 mm. with bleedings on the subconjunctiva and retrobular tissue. The sclera, cornea (9.2×8.0 mm.), anterior chamber and angle were normal. Slight congestion of iris, ciliary body, ciliary processes and choroidea was noticed and there was a bleeding area near the posterior pole. There was no infiltration of inflammatory cells in the uvea.The lens were normal. The pigment epithelial layer, rods and cones layer,internal and external molecular layer, internal and external granular layer of the retina were normal. The fiber and ganglion cell were absent in the nerve fiber layer and the ganglion cell layer, the capillaries had ruptured the inner limiting membrane, by endothelial proliferation, extending from the retina to the vitreous side near the nasal equatorial region in the nerve fiber layer. Beside this there were bleedings near the nasal ora serrata, temporal ora serrata and equatorial area of the nerve fiber layer. There was endothelial and glial proliferation just behind the ora serrata in the nerve

Table 1 General Findings in 15 Anencephalic Fetuses

Case	Sex	Body-weight (g)	Crown-rump (cm)	Crown-heel (cm)	Condition of Delivery	Survival Time	Presentation of Fetus at Delivery	Serological Test	Associated Malformation
1	♂	680	14.7	22.5	Stillbirth		Face	(—)	Spina bifida-
2	♀	935	20.8	32.9	〃				Abdominal
3	♀	1130	25.8	42.0	〃		Face	(—)	hernia ,Cor
4	♀	1420	25.0	46.3	〃				biloculare.
5	♀	1450	23.2	42.5	〃		Occiput		
6	♀	1740	25.5	41.5	〃				
7	♀	1800	27.3	43.8	〃				
8	♂	1900	27.2	48.5	〃		Occiput	(—)	Hydroneph-
9	♀	2000	24.3	45.0	Livebirth	11.5hrs.	Occiput	(—)	rosis.
10	♀	2020	28.1	45.1	Stillbirth				
11	♂	2100	32.8	48.0	〃		Occiput	(—)	
12	♂	2150	24.3	41.0	〃		Occiput	(—)	
13	♀	2400	29.7	59.5	〃		Face	(—)	
14	♂	2700	32.0	53.0	〃		Occiput	(±)	Polycysti-
15	♂	2760	32.0	46.4	〃				Kidney

fiber layer and the inner layer of the retina, accordingly the area was thickened twice as much as that of the normal. There was a hyaloid artery in the vitreous body in front of the optic disc. The optic disc was subsided remarkably and was lacking in nerve fiber, and only a trace of glial tissue was left.

Right eye: The size of the eye was 17.0×16.5 mm. There was a fairly large area of bleeding in the subconjunctiva and retrobular tissue.

The sclera, cornea (9.0×8.0 mm.), anterior chamber, angle, iris, ciliary body and ciliary body and ciliary processes were normal. The choroid was slightly congested but there was no infiltration of inflammatory cells. The pigment epithelial layer, rods and cones layer, internal and external molecular layer, internal and external granular layer of the retina were normal. The fiber and ganglion cells were absent in the nerve fiber layer and ganglion cell layer. In the nasal and temporal equatorial region equivalent to the nerve fiber layer there was a mass of vasoformative tissue due to the endothelial proliferation. This tissue invaded the vitreous body rupturing the inner limiting membrane. (Fig 1) Further the bud of capillaries extended to the side of the optic disc running along the retinal surface or invading the vitreous body (Fig. 2). There were subhyaloid or vitreous hemorrhages near the vasoformative tissue in the vitreous body and may new capillaries were invading the hemorrhage lesions from the retina (Fig. 3). The optic disc is remarkably subsided and was lacking optic nerve fiber.

Fig. 1 (Hirose and Yoshioka) Case 5. right eye. Budding of the vasoformative tissue from the nerve fiber layer to the vitreous.

Fig.1

Fig. 2 (Hirose and Yoshioka) Case 5. right eye. Vasoformative tissue in the vitreous.

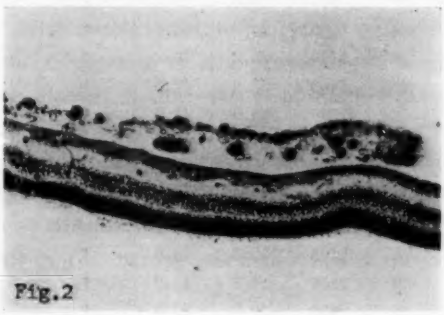

Fig.2

Fig. 3 (Hirose and Yoshioka)
Case 5. right eye. Bleeding in the vitreous and the new-formed vessels extending from the retina.

Fig. 4 (Hirose and Yoshioka)
Case 6. left eye.

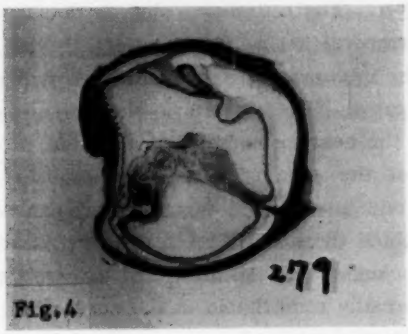

Fig. 5 (Hirose and Yoshioka)
Case 6. left eye. fibrotic retina and endothelial nodule in the retina behind the lens.

Fig. 6 (Hirose and Yoshioka)
Case 6. left eye fiberstrang from the optic disc extending into vitreous.

Case 6. Left eye (Fig. 4): The size of the eye was 17.2×15.5 m.m. There were bleedings in subconjunctival and orbital tissue. The cornea(9.5×7.4 m.m.), sclera, anterior chamber, angle, iris, ciliary body and ciliary processes were all normal. A slight

pupillary membrane was present. The choroid was slightly congested and extramedullary hematopiesis was noticed in some parts. There was no infiltration of inflammatory cells in the uvea. The lens was normal. The optic cells were atrophic in some parts. The internal and external molecular layer, internal and external granular layers were normal. The ganglion cell was absent in the nerve fiber and ganglion cell layer. The retina was slightly detached at the posterior pole near the optic disc. The temporal retina was also slightly detached extending to the ciliary body crossing over the ora serrata in the front. The dispigment epitheial cells in this area was slightly proliferated. There were no changes in any places of the ora serrata of the retina, but in the near an endothelial and glial proliferation was noticed in the nerve fiber layer of the equatorial region consequently showing a thickening. The retina of the nasal ora serrata and equatorial region was detached and protruded to the vitreous side behind the lens. The retina of this area abound in the fold with proliferation and thickening of each layer and its' arrangement was very irregular. The thickening was specially remarkable in the nerve fiber, and glial proliferation, nodules according to endothelial proliferation, new formation of capillaries which directly connected the new formation of capillaries in the vitreous body were noticed besides the fibrotic proliferation (Fig. 5). Though only one, an incomplete rosette was noticed.

With respect to other parts of the retina besides the previously mentioned, slight thickening, vacuole formation, slight glial and endothelial proliferation and new formation of capillaries were noticed in the nerve fiber layer of the nasal and temporal retina from the equatorial region to the optic disc. In the areas with such changes, a thin fibrotic tissue which contains a small number of cells extended from the retina to the vitreous body like a spreading hand. It stained yellow to van Gieson in front of the optic disc, and a fibrotic funiculus with slightly large blood vessels extended to the vitreous body the apex, of which as a group of coarse fiber, connected with the proliferated area of the nasal retina beforementioned. The retina near the optic disc adhered on both side of the funiculus and was like in a condition of being pulled and detached by the funiculus (Fig. 6) Specially the temporal retina was proliferated, thickened, and the structure was completely irregular. The optic nerve was thin in general without any optic nerve fiber, and was composed of irregulary arranged glial tissue. Congestion was remarkable.

Between the posterior and equatorial area of the lens and ciliary processes, there were distinct star shaped mesodermal cells with long processes that formed a net crossing each other. This is the so called retrolental membrane and between the previously mentioned proliferated area of the nasal retina, there were hemorrhages, phagocytes of hemosiderin, lymphocytes, new formed capillaries and fibroblasts noticed.

Right eye: The size of the eye was 17.5×15.6 mm. The cornea (9.7×7.5 mm) and sclera were normal. The anterior chamber was shallow with exudate. The development of the angle was normal. The iris, ciliary body and ciliary processes

were normal. A slight pupillary membrane was present. There was a degenerated solidified mass on the capsule of the posterior pole. A fairly large area of bleeding was noticed in the posterior pole of the choroid. There were no other remarkable changes. In the retina, the fiber and ganglion cells were absent in the nerve fiber layer and ganglion cell layer. Vacuole formation was noticed in a part of the nerve fiber layer. There were no other remarkable changes besides the hemorrhages in some part of the internal molecular layer. A slight hyaloid artery was present. The optic disc subsided remarkably and the central vessel inclined to one side. The nerve fiber was not noticed and there was an irregular glial tissue. The congestion was slight.

Discussion

A program whether the pathogenesis of retrolental fibroplasia is of a prenatal or postnatal origin. People who consider the pathogenesis of retrolental fibroplasia as of a postnatal origin base their opinion on the following facts and we like to discuss this a little and present our objection in the following.

1) The majority of the disease develops after a certain time from birth, accordingly the eye changes are not noticed in the newborns by the examination of eye-grounds[13)14)16)25)]. There was also no change by histological examination in stillborn infant's eyes[8)]. The objection to this is that the disease develops in the equatorial region of the eye and extends gradually to the retrobulbar retina and the vitreous body, consequently it is impossible to detect such early changes by ophthalmoscopic examination soon after the birth, because it is difficult to examine in the newborn and the change is very slight and the lesion is a difficult part for examination.

2) Clinically the disease develops often in premature infants inhaled with highly concentrated oxygen[21)] and similar eye changes can be produced experimentally in young animals by inhaling highly concentrated oxygen[1)2)15)17)]. They assert the postnatal origin seeking relation between the disease and oxygen. Objection to this is that there are reports which deny the relation between the disease and oxygen and there are cases in our country of late of the disease (including the so called retinal fold) which has no relation with oxygen inhalation[3)4)29)31)]. Suspecting that the eye changes similar to the disease can be produced in animal experiment, the changes are that of the early period and are not that of the clinical and pathological changes of early to the late period seen in human; consequently it is a question to identify it with the retrolental fibroplasia in man. Above are the points of argument on which they consider the disease to be of postnatal origin and our objections to this and we like to mention further more our positive ground which supports the prenatal opinion.

To consider the disease as of prenatal origin it is necessary to find the certain changes of the disease in eyes of newborns immediately after birth and it is difficult to find the changes clinically as mentioned before. Reese and others[20)] have found the early pathohistological changes of the disease in one case among 94 eyes of stillbirths,

premature and mature infants, and Yoshioka[27] one of our investigators has found the early histological changes in 2 eyes among 14 eyes of 14 premature infants who died soon after birth. These facts suggest that the bud of the disease had already existed in the eyes in the late embryonal period and is the ground to consider the disease as of prenatal origin. However, Reese and others[20] having mentioned as a mature birth anencephalus with a body weight of 1950 gm. with hypoplasia of the adrenal gland, reported (and Blodi) the same case as a 1950 gm, body weight infant, that died soon after birth[19] in 1951, and as a 1950 gm. body weight stillbirth infant, Reese, Blodi and Locke in 1952. It is uncertain whether the case was a stillbirth infant or not. Materials obtained by Yoshioka were of premature infants but was unable to exclude the relation of oxygen and the eye changes from the point of breathing air even for a short time. The materials obtained in this paper are of stillbirth-infants and attention should be paid on the point that there was no relation to the oxygen in the air. The pathohistological findings of our 1st case were similar to that of the case reported by Reese[1)5)6)8)9)19)20] and others and agrees with the early findings of the disease. In the 2nd case the proliferated thickened retinal tissue abounds in folds on the posterior side of the lens and agrees with the late findings of the disease[1)11)12)18)26)29]. There were no atrophy on other parts of the retina but rather a general thickening of nerve fiber layer. There were proliferations of endothelial cells and glial cells in this part and the pigment epithelial layer was fairly normal. These findings were somewhat different but such differences are of a periodical difference and considered as a late period of the disease.

As above mentioned we have noticed findings typical to that of an early period and close to that of the late period of retrolental fibroplasia in both eyes and one eye of stillbirth anencephalus and have made apparent that the disease is of a prenatal nature and has no relation to the oxygen in the air.

The relation between retrolental fibroplasia and endocrines. As already mentioned we have made apparent, that the disease is of prenatal origin and has no relation with oxygen and we like to touch further more on the question what is the cause of the disease. For this purpose we have investigated the changes of the eye in 15 anencepalus eyes or cases and their relation with pathohistological findings of other organs, specially in the two cases of retrolental fibroplasia. As anencephalus belongs to a particular category of malformation, the pathological findings of anencephalus is incomparable directly with that of the normal fetus. Thus pathological findings of anencephalus with retrolental fibroplasia and anencephalus without retrolental fibroplasia was compared. The common characteristic changes in anencephalus are the changes of endocrines and the cardiovascular system. As signs of cardiovascular disorder, congestions were noticed in various degrees in each parenchymal organ and endocrine. There was no particular difference in quantity and quality between the corpse with the disease and without the disease. Changes were noticed in all endocrine organs and

were specially remarkable in the hypophysis, thymus and adrenal glands[23]. Comparing these changes between the corpse with disease and without disease there was no particular difference in the hypophysis and thymus and showed an apparent difference in the adrenal gland. That is, the physiological degeneration (the cortex narrows by degeneration and medulla develops) of the adrenal cortex was noticed in both groups but the physiological degeneration of the fetal zone in the group with the disease was apparently delayed compared with that group without the disease. Previously Yoshioka[28] has mentioned the relation between the delayed physiological degeneration of the fetal zone of the adrenal cortex and retrolental fibroplasia. The results of our studies agree with it and is the ground to support the opinion strongly. However the question why the delayed physiological degeneration of the fetal zone in the adrenal cortex produces the disease, and what causes the delay, is still unclear and is expected to be elucidated in future study.

Summary

1. The eary and late pathohistological findings of retrolental fibroplasia was noticed in 3 eyes of 2 fetus among 15 stillbirth anencephalus cases. The pathogenesis was considered as of prenatal origin from the point, that eyes were obtained from unbreathed stillbirth fetus.

2. There is a close relation between the disease and the physiologic degeneration of the fetal zone.

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USE OF ANTHRANILIC ACID, A METABOLITE OF TRYPTOPHAN IN SIMPLE GLAUCOMA

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The treatment of glaucoma currently adopted in general may safely be considered to be the symptomatic therapy which aims the lowering of ocular tension. With regard to glaucoma of high tension, its therapeutic efficacy is undeniable on the whole, but the question is how it is about simple glaucoma, especially low tension glaucoma? It is a matter of course that this ocular-tension-lowering therapy is more or less effective in curing such cases as well, but this alone does not seem to be adequate enough for the complete prevention of progress of the disease.

Duke-Elder (1955) declared simple glaucoma to be "a sick eye in a sick body[1]. The author of this paper is disposed to think that what is of utmost importance in this connection is to give the whole sick body a careful consideration and thus work out a remedy.

For this purpose, the present author, besides hunting the related literatures extensively, took up the results previously obtained from glucose tolerance tests[7], intending thereby to establish a new kind of therapy. In consequence of it, the internal use of a modicum of anthranilic acid resulted in bringing about a lowered ocular tension and an improved visual field, simultaneously with these alleviation of bodily disorders. This note-worthy finding, although still unsatisfactory in not a few respects, is here reported as follows:

Materials and Methods

Patients. 7 simple glaucoma patients who were under treatment in the hospital attached to Wakayama Medical College. They were diagnosed as such, they not only revealed the cupping of the nerve head ophthalmoscopically, with Bjerrum's scotoma revealed in the visual field and more than 7 mmHg of phasic variation in tension, besides, but also because the above-mentioned glucose tolerance test produced results sufficiently indicative of glaucoma. From four (Case No. 2, 3, 4 and 7) of them, i. e. 8 eyes, positive results in accordance with Suda's bulbar pressure test were obtained. (Table 1.)

Methods of measurements.

1) Two dose glucose tolerance test: A dose of 30 gr of glucose was administered orally. 90 minutes thereafter, this oral administeration was repeated by employing as before. Before and after glucose administration, half-hourly blood glucose measurement was conducted in pursuit of the blood glucose change by King-Garner's method.

Table 1 Phases of Anthranilic Acid Effect upon Glaucoma.

Case No.	Age	Sex	Eye	Visual Acuity	Visual Field peripheral (min.-max.) before	Visual Field peripheral (min.-max.) after	Bjerrum's Scotoma besore	Bjerrum's Scotoma after	O.T.(mmHg) before	O.T.(mmHg) after	B.P.T. before	B.P.T. after	Glucose Tolerance Test before	Glucose Tolerance Test after	daily admin. dosis/kilo
1	26	M	R	0.1(1.0)	full	full	relative	disappears	36～50	20～23			(+)	(−)	1.0 mg
			L	0.1(1.0)	〃	〃	〃	〃	38～64	20～24					
2	20	F	R	0.1(1.2)	〃	〃	〃	〃	14～25	16～20	(+)		(+)	(−)	0.6 mg
			L	0.1(1.2)	〃	〃	〃	〃	14～25	17～19	(+)				
3*	65	F	R	0.08(n.c.)	35～50	45～69	?	?	21～24	21～25	(+)	(−)	(+)	(−)	0.2 mg
			L	0.08(n.c.)	30～55	40～70	?	?	24～34	22～25	(+)	(−)			
4	20	F	R	1.2	full	full	relative	disappears	19～29	18～21	(+)		(+)	(−)	0.6 mg
			L	1.2	〃	〃	〃	〃	19～27	18020	(+)				
5	61	F	R	0.1(n.c.)	37～72	50～80	〃	〃	16～25	15～20			(+)	(−)	0.2 mg
			L	0.6(1.0)	40～70	50～85	〃	〃	21～34	23～26					
6	59	M	R	0.5(1.0)	20～50	35～60	absolute ringscotoma	ennarrow, relative	24～35	23～30			(+)	(−)	0.2 mg
			L	1.0	40～80	50～85	relative	disappears	20～30	20～27					
7**	45	M	R	0.5(n.c.)	full	full	〃	〃	15～23	15～19	(+)	(−)	(+)	(−)	0.4 mg
			L	0.1(0.4)	〃	〃	〃	〃	15～23	15～19	(+)	(±)			

O.T. =ocular tension; B.P.T.=bulbar pressure test; each (+) or (−) means glaucoma positive or negative result.
The visual acuity was not changed by anthranilic acid abministration in all cases.
* accompanied with cataract, ** accompanied with trachomatous pannus.

2) Ocular tension: After having been prescribed to give up the use of mioticus not less than 24 hours at least, each of the patients was made to undergo tonometry with Schiotz's tonometer with 0.5% narcain instilled just before it, 6 times a day (at 6, 9 and 12 a.m. and 3, 6 and 9 p.m.) and the said tonometry was performed for a period of 4-7 succesive days till both ocular tension and phasic variation in tension reached their stationary state. Anthranilic acid was then administered by mouth and tonometry was again conducted as before.

3) Visual fields: Mostly during 10-12 in the morning, the patients were subjected to perimetry and campimetry in some light place.

4) Bulbar pressure test: Suda's method was adopted.

Internal use of anthranilic acid.

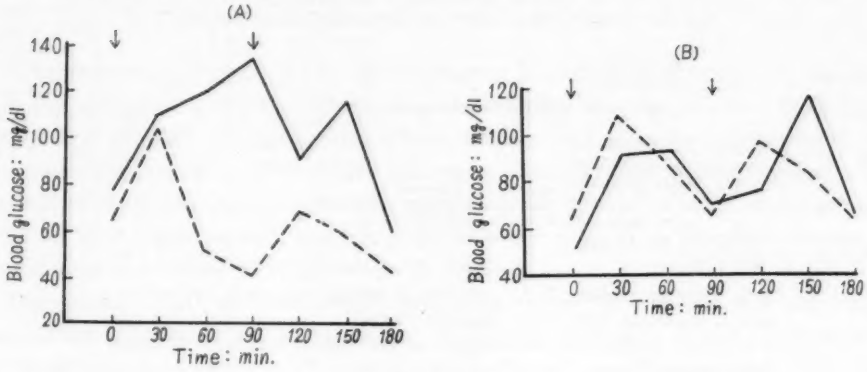
With regard to Case No. 1, a dose of 1.0 mg/kilo body weight was given three times a day, but as for the rest of the patients, the amount was reduced, i. e. 0.6 mg/kilo for younger patients, 0.4 mg/kilo for middle-aged one, and 0.2 mg/kilo for 3 older ones.

Results

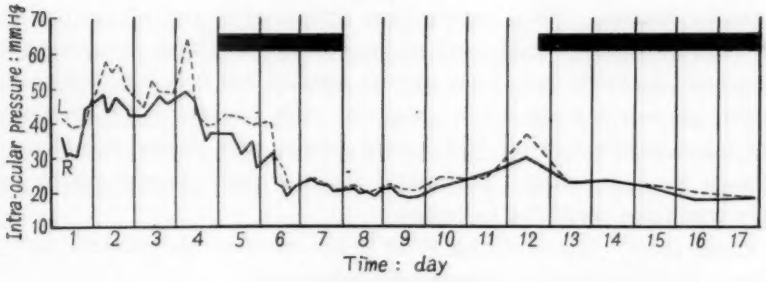
The internal use of anthranilic acid by the 7 simple glaucoma patients resulted as follows:

1) Two dose glucose tolerance test: One week after oral administration an improvement in the patients' tolerance could be detected without exception. Fig. 1 (A) and (B) shows the results obtained from Case No. 1 and 7, which were found to be typical examples.

Fig. 1 The two-dose glucose tolerance curves in regard to two glaucomatous patients administered with anthranilic acid.
The blood glucose subsequent to the dosing of 30 gr of glucose was measured half-hourly by King-Garner's method, full line standing for non-administration, and dotted line for administration of anthranilic acid, while (A) representing Case No. 1, and (B)Case No. 7. ↓: dosing of glucose.



Case No. 1



Case No. 7

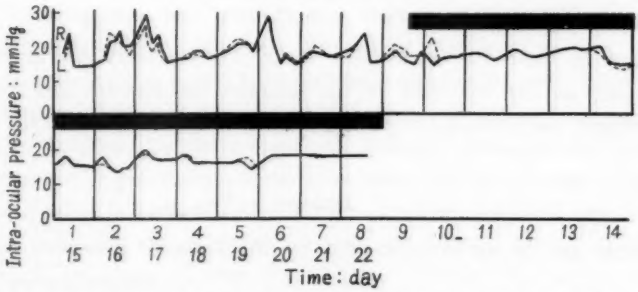


Fig. 2 The variation of intra-ocular pressure in regard to Case No. 1 and No. 7 administered with anthranilic acid.
The upper bold line represents the duration of administration, full line indicating the right eye, and dotted line the left eye. The intra-ocular pressure was measured in pursuit of phasic variation, but, in the case of No. 1, since the 10th day once at 9 a.m. only.

2) Ocular tension: After oral administration, ocular tension was found to fall gradually, accompanied with phasic variation in tension, till the tension reached its normal value two or three days later, simultaneously diminishing its usually excessive phasic variation. The fall was rather remarkable especially with regard to Nos. 1 and 4 (earlier cases of glaucoma), and although No. 2, 3 and 7 indicated a clearly noticable decrease, no such marked fall could be detected with regard to No. 6 (a later case of glaucoma).

Shown in Fig. 2 below are the results of lowered ocular tension and diminished phasic variation obtained from No. 1 and No. 7, which were found to be typical examples. Due to the discontinuance of the use of anthranilic acid, ocular tension seemed to rise gradually and the phasic variation to increase, on the other hand, about four to seven days thereafter (Fig. 2).

3) Visual field: Bjerrum's scotoma was found relatively or absolutely in all eyes of these glaucoma patients, except No. 3, but the use of anthranilic acid for seven to ten days resulted in its remarkable disappearance or reduction.

The peripheral visual fields of Nos. 3, 5 and 6 revealed either a slight or middle degree of centripetal defects, but they expanded by approximately 10°–15° in seven to ten days after anthranilic acid administration.

4) Bulbar pressure test: After anthranilic administration, this test was done with Nos. 3 and 7, but moderate or slight improvement was detected, with its normal value restored ten days thereafter.

Discussion.

The etiological cause of primary glaucoma is still unknown, but many scholars are of the opinion that it may not be a merely topical eye disease. On the present research-work from the same view-point, the following previous research reports came to my notice.

1) Schmelzer (1938) suggested its etiological cause to be a hindered metabolism due to a peculiar type of impaired liver function[11][12].

2) Kinugasa (1955) reported that he detected a slight degree of hemoglobin-decrease with regard to primary glaucoma patients[8]. Lately, this fact has been ascertained also by us.

3) Campbell, Gloster and Tonks (1955) reported that as compared with normally healthy people, primary glaucoma patients had their volume of diuresis reduced after they drank water[2].

4) Haselmann (1949) made a discovery that the sugar tolerance in primary glaucoma patients was slightly reduced as compared with nonglaucoma patients[6]. This fact was made sure also by us in 1955[7].

Meanwhile, anthranilic acid (o-aminobenzoic acid) employed in our clinic is a physiological intermediate metabolite of tryptophan which is an essential amino acid and easily changes in vivo into 5-OH-anthranilic acid. Kotake et al[9] discovered the

fact and further found this 5-OH-anthranilic acid to be capable of promoting liver functions, aiding urination, curing anemia and regulating blood sugar.

It might be possible to expect the cure of bodily symptoms in glaucoma patients, if we administered to them anthranilic acid which has the above-mentioned good effects on the whole body.

However, one of the evidences in this connection, a rising tendency of ocular tension can be detected unfailingly from No. 1 and No. 2 (not seen in Fig.) several days after the discontinuance of anthranilic acid administration. In view of the fact that especially No. 1 patient, who is one of the students of our Wakayama Medical College and has been under medical observation for more than nine months, often his oculor tension increased, when anthranilic acid administration was discontinued over about ten days, there seems to be no doubt about anthranilic acid effect of this sort. The recovery of normal visual fields may tentatively be considered to be due to the recovery of normal blood circulation in the retina resulting from lowered ocular tension, but probably it is not the sole cause of it, since No. 6 of no particularly lowered ocular tension showed a remarkable degree of expansion of this peripheral visual field.

Except for two instances of Nos. 3 and 7, besides what has been described above, anthranilic acid was considered to alleviate or completely cure glaucoma symptoms, and this was all the more presumable from the fact that Nos. 3 and 7, who, before the use of anthranilic acid, had produced positive or improved results as a result of a bulbar pressure test, revealed, after these negative results, in consequence of the same test. What was, such unmistakable improvement thru administration of anthranilic acid of the lowered tolerance, against the blood sugar of all the seven patients, as was discovered by Haselmann in 1955, is one of the unquestionable evidences of anthranilic acid effect.

By the bye, it must be added here, that in addition to the abovestated seven simple glaucoma patients, the effect of anthranilic acid had more or less satisfactory therapeutic efficacy, with regard to four eyes of three chronic congestive glaucoma patients, as well as in regard to four eyes of two brother and sister of hydrophthalmus, but two eyes of two acute congestive glaucoma patients and one case of secondary glaucoma produced no such good effect.

To sum up, the author of this paper, instead of taking recourse to operation or mioticus, to lower ocular tension, prescribed, as a remedy from the view-point of the "sick bodies" of simple glaucoma patients, the internal use of a modicum of anthranilic acid alone and succeeded, so far as the experiments were concerned, in curing their "sick eyes", thus attaining simultaneously the normalization of physical health.

As for the degree of lowering ocular tension, however, anthranilic acid is far less effective than "Diamox" or "Dibenzyline". But unlike these substances of toxic property, it is clearly a physiological one, notwithstanding the fact that the mechanism of its action is not known well. The slowness with which it lowers ocular tension,

however, seems to be a natural course of event, since it is considered that it changes in vivo into 5-OH-anthranilic acid and due to the redox-potential of oxydation generated with it, activates the weakened functions of internal organs.

From the results thus far enumerated, simple glaucoma can be concluded to be due to the disorder of the whole body, instead of being a merely topically ocular disorder. In this respect, the question of the liver, as pointed out by Schmelzer, seems to be of utmost importance. As a therapy for this disease, therefore, it is considered that as much or more importance should be attached to the cure of bodily symptoms such as the internal use of anthranilic acid than the instillation of mioticus or surgical operation.

Summary.

The author, prescribing the internal use of a modicum of anthranilic acid to the seven simple glaucoma patients under medical treatment, detected the complete normalization of their glucose tolerance in vivo, the lowering of their ocular tension, the decrease of phasic variation in tension and the improvement of their visual fields.

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CLINICAL SIGNIFICANCE OF THE MAXWELL'S SPOT

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The Maxwell's spot (MS) is considered along with Scheerer's phenomenon and Haidinger's brushes to be one of the entoptic phenomena which have relation to the foveal structure of the retina. This phenomenon was first described by J.C. Maxwell in 1856, and it has been investigated chiefly from physiologic curiosity. Recently, concerning its origin Walls and Mathews established a hypothesis of the foveal receptor-type distribution pattern ("RDP") giving rise to a new problem in physiology of vision. In ophthalmology, however, there have been only a few report on the test

for color-defectives and glaucomatous patients in addition to a few words by Miles in the Annual Reviews in 1955 on an assumption that minimal macular conditions such as edema, hemorrhage, exudate or cyst may interfere with the visibility of MS.

This work was done to investigate further possible clinical applications of MS which seem to be most favorable to the detection of the pathological process in the fovea because of the direct entoptic projection of its central region.

Methods

The method was essentially the same as that used by Miles and others. In front of the subject a light box with an opal glass window transilluminated by a 100 watt Mazda lamp stood at the level of the head. The distance from the observer's eye to the window was seat at 50 cm so that a tangent distance of 8, 75 mm on the opal glass corresponded to 1° in visual angle. The purple filter used was a piece of Wratten filter, No. 2398, 1 cm square in size, which was mounted edge to edge with a similar square of Wratten neutral gray filter, No. 96. The subject looked at the fixation point inked as a small cross at the center of the window alternately through the two filters.

Most normal observers see through the colored filter a reddish spot on a blue background. The normal MS score appears as a circular target card which typically consists of three parts: central spot (Area No. 3 by Miles), clearing (Area No. 2) and halo (Area No. 1).

Results

The patients with the following eye defects were examined: chorioretinitis centralis, macular atrophy, traumatic edema of the macula, retinal detachment, optic neuritis, optic atrophy, glaucoma, amblyopia, strabismus and so forth.

It was found from the review of 150 eyes having various kinds of ocular disease that there are a number of modifications that differ from the normal MS score more or less in their pattern, color and situation. Regarding them as subnormal MS scores, I classified them as follows:

A) Modifications of MS concerning pattern and color.

1) regular form 2) sub-regular form 3) irregular form 4) traces form 5) disappearing form

B) Modifications of MS concerning situation.

1) central form: those whose central position of MS correspond to the fixation point.

2) eccentric form or off center form: central position of MS deviates from the fixation point, shifting in a certain direction as upward, downward, inward, outward or oblique.

The present report deals with some of the ocular diseases examined.

1) MS in chorioretinitis centralis serosa (Masuda).

In most of the 22 cases of this macular lesion the visibility of MS deteriorated

and disappeared usually in the very early stage of the attack (disappearing form). At that time, the whole visual field over the opal glass window seemed dark violet or blue and occasionally ringed or cloudy shadow was observed on the background. With the recovery of symptoms, MS appeared again two weeks later at the earliest. In most cases, the outline of the surrounding area(Area No. 1) first became visible (traces form), followed in the next stage by the development of a red color which progressed centripetally, and then in the course of convalescence the above mentioned forms of the various step could be observed. When the development of MS score progresses smoothly, the regular form (normal MS score) can be seen again in about a month. But as a rule it requires so long a time for complete recovery that numerous cases come to a stop in an irregular or sub-regular form which leaves a dim area near the central spot. Such a tendency is marked particularly in cases where recurrences are repeated. There were a few cases where development of the score, beginning from the center, progressed centrifugally.

2) MS in squint or amblyopia ex anopsia.

In amblyopia ex anopsia which shows no visible fundus defect, the visibility of MS was truly different from that in organic lesion, such as chorioretinitis centralis. The most remarkable modification was in its situation; in convergent squint, 15 of 23 cases corresponded to the eccentric form, and in divergent squint, 11 of 24 cases corresponded to it. Namely, in the former the MS was observed to shift inward and in the latter to shift outward from the fixation point. In addition, in some cases of squint, in 6 of 18 cases of esotropia and 13 of 16 cases of exotropia, a shift of MS to a vertical direction was also seen. The distance of shift measured by the diameter from the fixation point to the central position of MS was 2 mm (less than 20′) at the shortest, and 15 mm (1° 40′) at the longest, being 5, 8 mm to 7, 5 mm (40′ to 50′) in most cases. When the calibration was done repeatedly, it was found that in one group the distance varied moment to moment, in another group it remained nearly constant.

Discussion

The MS is attributed by most investigators to absorption of the blue component of the light by yellow macular pigment. First I have compared to the subnormal MS score in chorioretinitis centralis with ophthalmoscopic findings including the macular edema or slight pigmentation in the fovea. But it was not possible to obtain any evidence favorable to the pigment etiology of MS. Next I have compared it with the response of the red and blue receptors in the fovea with the aid of electrical excitability by Motokawa. As a result, it was found that the noticeable decline in the red process was enough to corroborate the deterioration of the visibility of MS. This result, together with Isobe's experimental result, causes us to admit the hypothesis of Walls who sought the etiology of MS in the photoreceptor itself. At the same time it suggests

the primary participation of the lesion of the photoreceptor in chorioretinitis centralis. On the other hand, the data on routine examinations such as visual acuity, scotomas and color vision revealed the relationship with MS scores to a certain degree, though it was not always parallel. Thus, the test was proved to be of great value as a synthetic indicator of macular function. In the same way it has been confirmed that the test might be capable of application not only to central serous retinitis, but also to many other diseases involving macula.

There has been no report in which the phenomenon of the deviating entoptic figure in cases of squint is pointed out with clear explanation. Therefore it is worth noting that the deviation of MS inward in esotropia and outward in exotropia was found in a large proportion of cases. The fact that by use of this test we found among patients usually treated as horizontal squint many cases associated with the vertical deviation is also meaningful, because the percentage agrees with the recent statistics on the vertical component associated with horizontal squint. Furthermore, it is very useful to the diagnosis of eccentric fixation in amblyopia ex anopsia and degree of eccentricity or depth of amblyopia that we can measure the distance between the fixation point and MS presented to a small degree, and whether the distance is always constant or not gives us a new mean to estimate the unsteady fixation, the weakness of fixation power, or the existence of false macula. The next report with details will show the considerable practical importance of MS as a new test for the functional structure of the fovea.

Summary

With the purpose of making a clinical application of the Maxwell's spot which is one of the foveal entoptic phenomena, examinations were made of the visibility of the MS in various kinds of ocular disease, following the Miles' method of using purplish Wratten filter No. 2389.

As a result of the test I found, in addition to the MS known in physiology, various forms of scores which might be regarded as subnormal. I classified them accoding to their modification in patten, color and situation and studied their relation to the clinical course, visual acuity, etc.

It is usual for the MS to disappear at an early stage in some retinal lesions, especially in the chorioretinitis centralis (Masuda) and to appear again in the course of convalescence, and it is useful in an early detection of the involvement of the macular area and in the determining of complete recovery, as the development of scores lar can be observed at various stages.

Frequently in the case of strabismus, the MS was observed to shift from the fixation point in a certain direction, outward in exotropia and inward in esotropia. Moreover, the MS test gives us a new technique for detecting the vertical component

associated with the horizontal squint and for estimating the unsteady or eccentric fixation in amblyopia ex anopsia.

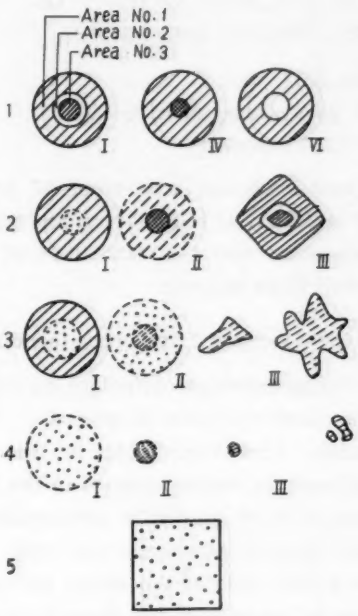

Fig. 1 —Modifications of MS concerning pattern and color.
1. regular form (normal form), 2. sub-regular form, 3. irregular form, 4. traces form, 5. disappearing form.

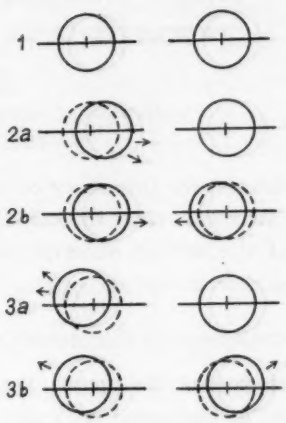

Fig. 2 —Modifications of MS concerning situation.
1. central form,
2—3. eccentric form: 2 a-b. deviation of MS inward in esotropia; 3 a-b. outward and upward in exotropia; a. unilateral, b. bilateral.

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HISTOLOGICAL STUDIES ON OCULAR STRUCTURES OF FETUSES IN THE DEVELOPMENTAL STAGE OF THE LATER HALF OF GESTATION
REPORT 1. OBSERVATION ON THE DEVELOPMENT OF PIGMENTED CELLS OF THE CHOROID AND SCLERA

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The material for this study covered 80 eyes made available from 67 fetuses that ranged in their eyes from the 4th month of gestation to the full term and the new-born infant, and the author observed the development and the distribution of pigmented cells of the choroid and the sclera. The result is as follows:

The Development of Pigmented Cells and the Subsequent Transition in Number.

On each part of the eyeball, there is a sharp individual difference on the monthly development of pigmented cells and the subsequent transition in number.

Table 1 and Table 2 show the mean value. From these tables we can know that the first developmented cells of the choroid and the sclera appears in the 5th month of gestation, when they have been specialized so much as can be distinguished. It is found in 1/3 of the area of th optic side of the choroid, and pigmented cells, increasing in number, spread in the aequator part, the optic side of the sclera and some more in the aequator part of the sclera. Therefore in the case of the choroid of the eyeball

Table 1

mean in cutting sagittaly

month age	upper side: 1/3 area of the cornea	upper side: 1/3 area of the aequator part	upper side: 1/3 area of the optic side		lower side: 1/3 area of theo ptic side	lower side: 1/3 area of the aequator part	lower side: 1/3 area of the cornea
4	0	0	0	Choroid	0	0	0
	0	0	0	Sclera	0	0	0
5	0	1.9	6.1	Choroid	6.9	3.0	0.3
	0	0.6	1.5	Sclera	1.9	1.0	0
6	1.0	8.3	20.0	Choroid	26.7	8.7	0.7
	0	2.0	4.7	Sclera	5.0	2.3	0
7	0.8	13.8	50.0	Choroid	38.0	17.7	0.8
	0.2	3.0	10.3	Sclera	8.3	2.0	0.2
8	7.8	71.3	109.0	Choroid	116.5	72.8	8.3
	1.5	3.3	17.7	Sclera	15.2	3.3	1.2
9	144.3	176.2	240.3	Choroid	171.5	165.3	122.7
	2.2	5.0	24.0	Sclera	21.2	4.5	3.2
10	138.0	242.0	382.0	Choroid	405.2	225.0	125.0
	3.0	12.0	40.0	Sclera	34.0	10.0	3.0
new-born infant	198.0	367.5	524.0	Choroid	433.5	360.5	215.0
	3.5	10.0	60.5	Sclera	59.5	10.0	4.0

Table 2

	month age	nasal side				temporal side		
		1/3 area of the cornea	1/3 area of the aequator part	1/3 area of the optic side		1/3 area of the optic side	1/3 area of the aequator part	1/3 area of the cornea
mean in cutting horizontally	4	0	0	0	Choroid	0	0	0
		0	0	0	Sclera	0	0	0
	5	0	2.2	6.2	Choroid	9.2	4.2	0.8
		0	0.6	1.4	Sclera	2.4	1.4	0
	6	0.7	10.3	32.0	Choroid	26.3	38.7	1.0
		0	2.7	11.7	Sclera	9.7	7.7	0
	7	7.3	42.0	48.3	Choroid	67.5	71.3	27.3
		1.3	5.3	9.5	Sclera	12.5	6.0	2.0
	8	8.5	70.8	81.3	Choroid	112.5	96.5	10.5
		3.0	12.3	16.8	Sclera	24.3	22.3	3.0
	9	87.4	196.6	292.8	Choroid	358.2	321.4	117.2
		3.2	7.2	32.2	Sclera	49.6	9.6	4.2
	10	81.7	265.0	349.3	Choroid	420.7	337.7	155.0
		3.8	12.0	34.0	Sclera	36.3	15.3	5.3
	new-born infant	194.0	386.0	472.5	Choroid	516.5	429.5	217.5
		3.0	8.5	56.0	Sclera	73.5	19.0	6.0

Table 3

Pigment / month age	Choroid			Sclera		
	1/3 area of the cornea	1/3 area of the aequator part	1/3 area of the optic Side	1/3 area of the cornea	1/3 area of the aequator part	1/3 area of the optic Side
4	0 −	0 −	0 −	0 −	0 −	0 −
5	0.3 (±)	2.8 (+)	7.1 +	0 −	0.9 (±)	1.8 (+)
6	1.2 (+)	16.5 +	48.0 ++	0 −	3.7 (+)	7.8 +
7	9.1 +	36.2 ++	51.0 +++	0.9 (±)	4.2 (+)	10.1 +
8	9.0 +	77.9 +++	107.3 ++	2.3 (+)	10.3 +	18.5 +
9	117.9 ++	214.9 +++	265.7 +++	3.2 (+)	6.6 +	32.0 ++
10	124.9 ++	267.4 +++	389.3 ++++	3.8 (+)	12.3 +	36.1 ++
new-born infant	206.3 +++	385.9 ++++	486.6 ++++	4.2 (+)	11.9 +	62.4 +++

less 1	(±)	101 ~ 200	++
less 5	(+)	201 ~ 250	+++
6 ~ 20	+	251 ~ 300	+++
21 ~ 50	++	301 ~ 400	+++
51 ~ 100	+++	401 ~	++++

of the 5 months-old fetus, the developmental frequency of pigmented cells is superior on the lower side and the temporal side of the choroid to that on the upper side and

the nasal side of the other. Sometimes pigmented cells are seen in 1/3 area of the cornea. While in the case of the sclera the same as the above can be said, but compared with the former the latter contains less pigmented cells, especially in 1/3 area of the cornea the author can find no pigmented cells in any eyes.

Even when the fetus becomes more than 6 months old, the pigmented cells are found more on the temporal side than on the nasal side, but the difference in number betweeen those on the upper side and those on the lower side is not always constant.

It seems to have a tendency that in the 5th or 6th month, they can be found more on the lower side and that with each advancing month they increase more on the upper than the cells on the lower side.

From table 3, without distinction of the upper side, the lower side, the nasal side or the temporal side of the eye-ball, the pigmented cells are most abundant in the 1/3 area of the optic side of the choroid and the sclera; to the front side from there they become less throughout the entire period of the fetus. Moreover, From the 1/3 area of the optic side to that of the aequator part a rapid decrease of them can be observed on both membranes till the 7th month, and thereafter they gradually decrease; from the 1/3 area of the aequator part to that of the cornea, till the 8th month and then gradually.

Next investigating the developmental condition of the pigmented cells in each region, the author has rarely observed them in the 1/3 area of the cernea of the choroid in the 5th or 6th month; on almost every eye in the 7th or 8th month; as many cells as on 1/3 of the area of the optic side in the 8th month after the 9th month. In the 1/3 area of the aequator and the optic side, the pigmented cells, apparently occurring in the 5th month, increase every month and especially in the 1/3 area of the optic side their increase is rapid.

While in 1/3 area of the cornea of the sclera, they are never seen till the 6th month; only a few cells from the 6th month to new-born baby, that is, as many as can often be found in the cornea of the choroid in the 5th or 6th month. In the aequator part and the optic side of the sclera in the 6th or 7th month these cells surely occur and, then gradually increasing, in the 9th month, they reach almost as many cells as in 1/3 of the area of the optic side and that of the aequator part in the 6th month.

Both in the case of the choroid and the sclera, the rapid increase of the pigmented cells is seen at first between the 8th and 9th month, next in the period of the new-born infant. Of course the pigmented cells of the choroid are superior in number to those of the sclera on every part throughout the entire period, but there is only a little difference till the 5th or 6th month. With increase of month age there appears a large difference and in the 10th month it sinks below (less) 1/10. Therefore, in case of the new-born infant, the absolute difference of the number of those between both membranes becomes larger and larger; while the ratio of number, smaller from the 1/3 area of the cornea to that of the aequator part; a little larger in the 1/3 area of the optic

side ; comparatively larger in that sclera.

Monthly Change of Pigmeted Cells.

The author divided pigmented cells into 2 parts in size—the small one under 40μ and the big one above it. The following is the result about the change of the number of the cells in these two parts.

Regardless of the optic side, the aequator part, the corneal side of both membranes or the upper, the lower, the nasal, the temporal side, in the 5th month only the small cells are found but after the 6th month the big cells are inclined to increase with each month of age. Between the 8th month and the 9th the big cells become as many as the small ones ; in the 10th month the former is superior to the latter. There lies a little difference in the developmental condition, of each side of the eyeball, that is, in the upper and the lower side a rectilineal increase is seen with advance of the month age, while in the nasal side and the temporal side the cells don't increase for a while between the 6th month and the 8th.

On the Form of the Pigmented Cells the Change of the Granule and the Grouping of the Cells with Month Age.

In the 5th month the pigmented cells are all the smallest longspindle shaped ones, and the granule contained in them is very minute, small quantity and light-brown. In the 6th month a few multi-processus-cells appear around the optic nerve. Thereafter they have an inclination to increase gradually with the advance of the month. Consequently the granule becomes rougher and darker and after the 9th month, being in large quantities, the cells themselves become bigger. But the promontory is enlarged and comes to contain pigmented granules densely in it.

In the 9th month there appears a tendency to make groups among the pigmented cells from the optic side to the aequator part, then to be larger ones with advance of the month.

Comparison

Comparing the report of the author with that of others, the month of the development of the pigmented cells is, according to my observation, the first stage of the 5th month of the fetus in both membranes. This is one or two months earlier compared with the report of foreign scholars ; as many later compared with that of Japanese scholars such as Seki and Kō, and is in accord with Yamagata's. Both Seki and Kō report that the pigmented cells are found earlier in the sclera than in the choroid, but according to my observation, it is the contrary.

The pigmented cells in both membranes appear around the opticside or nerve, this observation of mine is approximately in accordance with that of Kō's.

Accordingly, in the case of the eyeballs of the fetus the pigmented cells are dense around the optic side and gradually become sparse to the 1/3 area of the front aequator part and that of the cornea, with Nakamae's one about the adults, this is quite in

accordance with the observation of Kō, Seki and others, also with that of Nakamae who investigated eyeballs of the adults.

The period of the development of the pigmented cells in the 1/3 area, of the cornea lies, according to my case, in the 5th month in the case of the choroid; in the 7th month in the case of the sclera. But Kō says, that it is in the later stage of the 6th month. In his observation the pigmented cells decrease in number till the 7th month when they move from the aequator part to the 1/3 area of the cornea, but in mine, a month earlier, and such state has continued till the 8th month. More in the part from the 1/3 area of the optic side to that of the aequator part, there is found the rapid decrease of cells till the 7th month. Next, observing the difference of the pigmented cells on each side of both membranes, Segi says that in the firist stage (4th month) of the fetus they are superior in the temporal side to the nasal side; in the lower side to the upper side. The author has got the same result in the 5th month eye-ball, and has found, that after the 6th month they have a tendency to be superior in the upper side to the lower side, though the differences between the nasal side and the temporal side are the same as in the 5th month eye-ball.

Further about the size of the pigmented cells, Kō says that from the 3rd to the 4th month there are found many of 50μ or so, sometimes larger than that, but I have found that they, being all small ones less than 40μ until the 5th month, become the ones that are more than 40μ in the 6th month and increase their size with the advauce of the month age.

In short, in the case of the eyeballs of fetuses in Southern Kyushu the period of the pigmented cells' apparance in both membranes is earlier than those in foreign countries, one or two months later than those of other Japanese. They appear in the choroid earlier than in the sclera. The quantitative relations of the pigmented cells on each of the eyeball is the same as that of Kō in the 5th month.

But it has been found, that after the 6th month of fetus they are superior at the nasal side to that of the temporal side; on the upper side, to that of the lower side.

Fig. 1 The optic side of 4-month-old-fetus near the crystalline lens.

Fig. 2 The aequator of 5-month-old-fetus near the crystalline lens.

Fig. 3 1/3 area of the optic side of 6-month-old fetus.

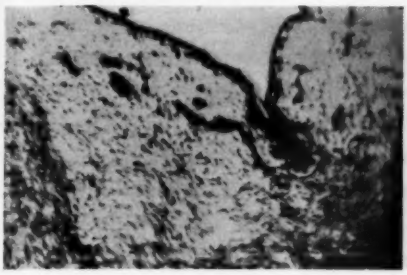


Fig. 4 Near the optic side of 7-month-old fetus.

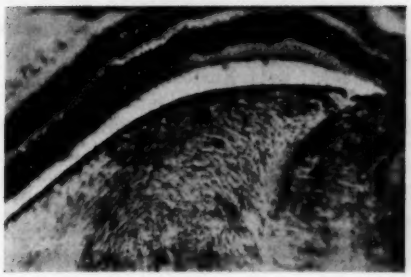


Fig. 5 1/3 area of the optic side of 8-month-old fetus.

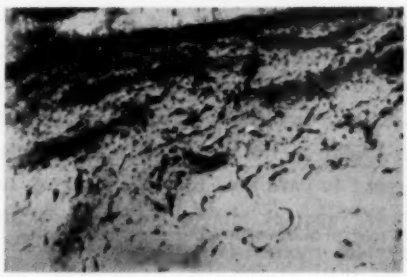


Fig. 5 1/3 area of the optic side of 9-month-old fetus.

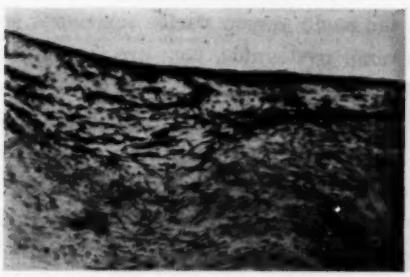
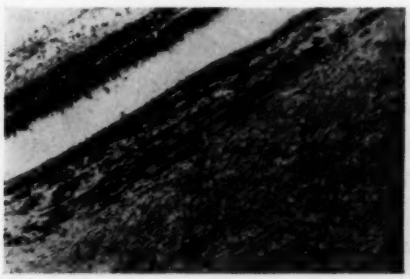


Fig. 7 1/3 area of the optic side of 10-month-old fetus.

Fig. 8 1/3 area of the aequator of 10-month-old fetus.



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OBJECTIVE MEASUREMENT OF THE LIMIT OF UNIOCULAR MOVEMENT

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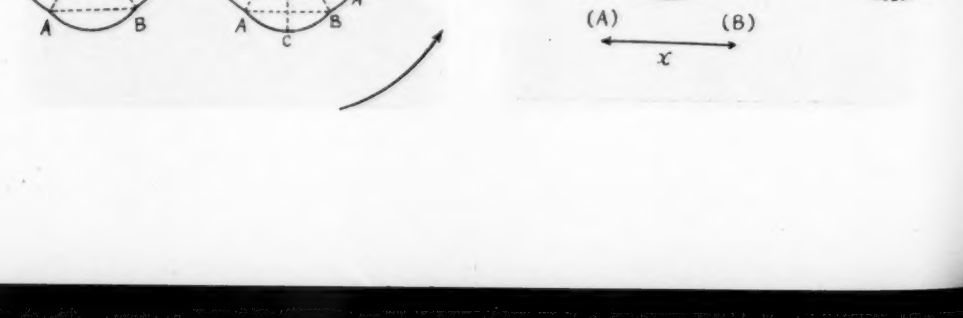
The measuremnt of the maximal version of the eyeball in voluntary movement is accompanied by considerable difficulty. For instance, besides the many obstacle that are present in the method of measurement, the maximal version of the eyeball of the same person varies somewhat from day to day, and errors due to physiological terminal nystagmus, etc., are inevitable even when the examiner is skilled and the subject is cooperative. The measurement of the field of fixation is a comparatively simple in method. But it lacks the reliability enjoyed in objective measurement. This is a fundamental defect, and in some cases the bridge of the nose obstructs the measurement. Some of the objective methods described to date, are illogical, making only approximate measurements, while others require special instruments manufactured for this very purpose. A simple and satisfactory method is not to be found. The author has tried a new method using a ready-manufactured diagnostic instrument. Measurements were taken on 200 eyes of 100 persons whose position and motility of the eyeballs are quite normal. The results are presented here.

Method

Principle of Measurement Method.

Fig. 1



1) Calculation of Angle from Liner Measurements on the Basis of Stevens' Hypothesis (Refer to Fig. 1).

According to Stevens' hypothesis, the three points, that is, the center of rotation (R), and each end of the corneal diameter (A,B) are located at equal distance from each other (the distance is approximately 12 mm), Δ RAB is an equilateral triangle. Terefore, AB=RA=RB, $\angle ARB=60^\circ$. When the eyeball rotates about the fixed point R, Δ RAB becomes Δ RA' B'. Where the center of the cornea is C, the base of perpendicular drawn from A' on RC is C', $\angle A'RC$ is θ, AB is x and A'C'is y, the angle of rotation ($\angle ARA' = \angle BRB'$) can be formularized as below:

$$\angle ARA' = \angle ARC + \angle A'RC = \frac{\angle ARB}{2} + \theta = 30^\circ + \theta$$

At ΔRA'C',

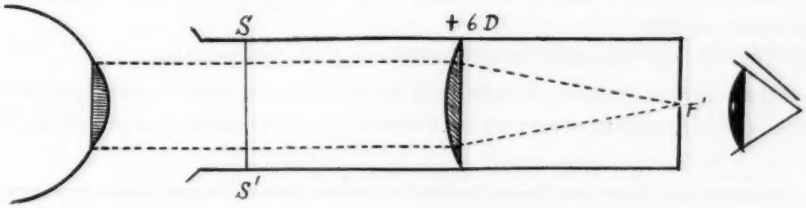
$$A'C' = RA' \sin\theta$$

$$y = x \sin\theta$$

Therefore, if the lines x and y are measured, the angle of rotation can be calculated.

2) Avoidance of Observational Error by Wessely's Keratometer (Refer to Fig. 2)

Fig. 2



Because of its characteristic of observing parallel light rays observational errors due to variation in distance between the instrument and the object do not occur within a certain distance with Wessely's Keratometer.

Therefore, at the time of the rotation of the eyeball, observational erros of linear measurement due to the variation of distance between the instrument and limbus can be avoided by the use of this Keratometer.

Actual Measurement by Keratometer. Fix the head of the subject to the head-rest by a band to prevent it from moving and also fix a pilot lamp 5 meters directly in front of the eye which is not to be measured. Then, place the Wesseley's Keratometer horizontally fixed on a stand that permits free movement, just directly in front of the eye to be measured allowing 3 cm from this eye to the tip of the Keratometer. In this measurement the distance between the tip of the Keratometer and the vertex of the cornea, need not be exact as stated in item 2 of "Principle of Measurement Method", above, but the reason for fixing the distance is to perform a measurement under the same condition.

Firstly, put the meter horizontally and measure the horizontal diameter of the cornea (x mm.). Adjust the position of Keratometer so that zero graduation is aligned

with the center of the horizontal diameter of the cornea. The eye to be measured is adducted as much as possible and the position of the temporal limbus of the cornea (y mm.) is measured. Then, after the other eye has been fixed on the poilot lamp, abduct the eye to be measured to the greatest degree, and measure the position of nasal limbus (y mm.). Turn the Keratometer perpendicularly and measure the vertical diameter of the cornea (x mm). Align the point of zero of meter to the center of the vertical diameter of the cornea and measure both the lower and upper limbuses (y mm.) at maximum elevation and depression respectively. At this time, the examiner should use his fingers to manipulate the lid of the eye being measured to allow the measurement to be taken.

Subject. Persons whose eyes are normal in poise and motility of eyeball, were selected as the subjects.

Results

The results are shown by degrees of the angle calculated from the above measurement values and in these results the figures of a degree less than 30′ were discarded and 30′ and over were raised to one degree. The mean values were adjusted to the nearest whole number.

The Limit of the Movement in 4 Directions and the Mean Value.

1) The limits of angular momentums in 4 directions, that is, adduction, abduction, elevation and depression measured on 200 eyes of 100 persons, are shown in Table 1.

Table 1 The Limits of Angular Movement

	Maximum Angle		Minimum Angle		Average Angle		
	Right Eye	Left Eye	Right Eye	Left Eye	Right Eye	Left Eye	200 Eyes
Adduction	68°	66°	47°	50°	57°	58°	58°
Abduction	63°	62°	40°	45°	53°	52°	53°
Depression	62°	60°	31°	33°	50°	49°	50°
Elevation	55°	56°	31°	33°	42°	42°	42°

This table shows a considerable difference in respective maximum and minimum motion in each direction. This shows that there is remarkable individual difference. In a person whose angle of maximum rotation in one direction is large, the maximum angles in other directions are also large. Likewise if the angle of maximum rotation in one direction is small, the maximum angles in other directions are also small.

2) In the mean values, though there is a slight difference between the right and left eye, it is found that in both eyes the value of adduction is largest, abduction next, depression next and the value of elevation is smallest.

3) However, as for the individual eye, the above order is not always found. The relation of the angle of maximum rotation in opposite directions (i.e. adduction and

abduction, and elevation and depression) is shown in Table 2.

Maximum Angle of Movement and Age of Person. When the maximum angles are measured according to age groups of 10-19, 20-29, 30-39, 40-49 and over 50, (those examined ranged in age from 11 to 81 years) it was found that the angle decreases with few exceptions, little by little till 50 years of age. And especially over 50 years, a remarkable decrease occurs as showm in Table 3.

Table 2 The Relation of More of Less of Maximum Rotation Angles in the Respective Opposite Directions

Adduction > Abduction	153 eyes	Elevation < Depression	175 eyes
Adduction = Abduction	35 〃	Elevation = Depression	13 〃
Adduction < Abduction	12 〃	Elevation > Depression	11 〃

Table 3 Maximum Angle of Movement and Age of Person

Direction / Age	Right Eye				Left Eye			
	Adduction	Abduction	Depression	Elevation	Adduction	Abduction	Depression	Elevation
10~19(24 persons)	58°	54°	51°	44°	60°	53°	51°	43°
20~29(33 〃)	57°	54°	51°	42°	59°	52°	50°	41°
30~39(13 〃)	57°	52°	49°	42°	59°	52°	49°	41°
40~49(17 〃)	57°	53°	49°	41°	58°	52°	49°	41°
50~ (13 〃)	54°	52°	46°	39°	55°	43°	43°	39°

Maximum Angle of Movement and Sex. No difference can be seen between the sexes in the measurement values of 49 males and 51 females.

Maximu Angle of Movement and Ocular Dominance. Of the 100 persons, the maximum angle of movement of each eye was compared respectively in each direction in 82 persons who have evident ocular dominance. There are 124 cases in which the dominat eye's maximum angle is larger, 104 cases, where the dominant eye's is smaller and 100 cases in which there is no difference. No definite tendency in this respect could be found. The examination of ocular dominance was performed in accordance with the revised Rosenbach method.

Consideration

The Method of Objective Measurement of the Limit of Uniocular Movement. Many methods of objective measurement have been presented up to date. But in these methods accurate measurement depends upon special and complicated instruments,

while the more simple methods give only approximate measurement values. As a method of angular measurement, the measurement by perimeter is simple, in which the image of a luminous point on the cornea is to be used, but error due to eye-measurement is inevitable. T. TSUBOI has presented in Japan the method of measurement by the use of a curved meter. The radius of the eye-wall rotation is the curvature radius of this instrument. Before this, T. DODO having intended to made an angular measurement, suggested that the instrument for observation of parallel-rays be equipped with a graduated scale made by the tangential projection of the angular division points of a semicircle, the radius of which is the distance from the center of rotation to this limbus. But actual results are not stated in either of the above mentioned methods.

Stevens' Tropometer is another instrument to measure the angles directly and its principle is based on the same hypothesis as that of the experimental method the writer adopted.

The scale of angle graduated by tangential projection of the points divided at 10° intervals (from 0° to 90°) of the circumference was fitted within the cylinder of the telescope.

After adjustment is made so that the corneal image of the subject can be observed just between 0° and 60° of the Tropometer, the associated movement of the eyes should be exerted to the utmost and the anglar degree of the position of the limbus should be read directly on this meter. In my early experience, however, when the writer tried this method to directly measure the angle by using the scale on which angular graduation has been made by means of tangential projection on the dividing points, it was found, that it has a disadvantage in that the intervals of graduation around 90° become so narrow that the observational error is large, particularly large when terminl nystagmus is present. Therefore, the writer used the Wessely's Keratometer with graduation in mm. Accurate linear measurement was taken, avoiding observational errors as much as possible after having completely fixed the subject's head and the Keratometer. Then the writer calculated the angles logically on the basis of Stevens' hypothesis as mentioned hitherto.

Results of Measurement. There are few descriptions on the actual results of objective mesurement. According to the results of Stevens' measurement by using the Tropometer, the maximum angles are 48°-53° in abduction, 48°-53° in adduction, 50° in depression and 33° in elevation. In the measurement results of Davson, who used a Perimeter, angles of adduction, abduction and depression were found to be approximately equal, i.e. 50°-60° and 40°-50° in elevation.

For the purpose of comparison, there are many reports on the actual subjectivemeasurement on the field of uniocular fixation. Graefe has reported 44° in adduction, 38° in abduction, 55° in elevation and depression. KIHARA has stated that when measuring 20 Japanese, the mean values of the field of uniocul fixation are 30° in adduction, 48°

in abduction, 59° in elevation and 50° in depression. KATSURA has also reported as the mean measurement values of 20 Japanese, 49° in adduction, 53° in abduction, 41° in elevation and 57° in depression.

When the writer's measurement values for 100 eyes i.e. 50 left and 50 right in 4 directions, are expressed in the histogram, each curve for the 4 directions approximates the normal distribution curve. However it is found that the distribution curve in case of abduction and adduction tends to rise more sharply than in case of elevation and depression. And in the comparison of the mean values 100 right and left eyes in each direction, they are nearly the same with the maximum difference being only 1°. In the mean values for all 200 eyes, adduction is the largest being 58° followed by abduction 53°, depression 50° and then elevation 42°.

As for the age and sex of the subject and the angle of rotation of the eye, it has been reported, that on measurement of field of uniocular fixation there is no difference due to sex, and the angle of rotation of the older subject is smaller than that of the younger suject. These facts can also be observed in the writer's measurement results. There is no literature on correlation of rotation angles with ocular dominance. In the writer's examination results, no relation could be observed.

Conclusion

1. I have reported on a simple method of objective measurement for investigation of the limit of uniocular movement by angular unit. In this method, two measurement values mentioned below, should be converted into the angular units in accordance with Stevens' hypothesis after the accurate linear measurement with Wessely's Keratometer has been obtained. The masurement values are:

(a) Corneal diameter and

(b) The distance at the frontal plane between the corneal center looking straight forward and the limbus farthest from the ocular angle at maximum rotation.

2. 200 eyes of 100 persons whose position and movement of the eyeball were normal, were measured to determine the limit of the associated movement in 4 directions, i.e. adduction, abduction, elevation and depression.

3. The results were as follows:

(1) As for the movements in 4 directions, there is a considerable difference between the maximum and minimum angles movement.

(2) The average maximum angle of rotation in 4 directions are 58° in adduction, 53° in abduction, 50° in depression and 42° in elevation.

(3) The maximum angle has an inclination to decrease as the age advances.

(4) There is no significant difference in the maximum angle between the sexes.

(5) The maximum angle has no connection with the ocular deminance.

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STUDIES ON THE AUTONOMIC EYE PRESSURE ADJUSTMENT FUNCTION OF NORMAL EYE

Part 1. Studies on the Autonomic Eye Pressure Adjustment Center

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I. Existence of the autonomic eye pressure adjustment function

Glaucoma has been of the most important and interesting problems in recent ophthalmology. The author has been studying this subject, especially the etiology of glaucoma, for the past 10 years.

First of all, the mechanism controling intraocular pressure has been investigated from several points. Some important physiological functions, such as blood pressure, cardiac and respiratory rate and so on, are controled automatically by an autonomic nervous system, however little is known about what controls intraocular pressure. Many attempts have been made to demonstrate the autonomic eye pressure adjustment functions as the basic and fundamental problems in our serial studies on glaucoma.

1) The relations between general blood pressure and intraocular pressure

Although there are a considerable number of works on the relationships between general blood pressure and intraocular pressure, many aspects of this connection remain unclear. (v. Hippel. u, Grünhagen[1]. Wessely[2], Wegner[3], Barany[4], Yada[5], Tamura[6]). The author has investigated this problem clinically and experimentally.

Age and intraocular pressure. It is generally accepted that blood pressure increases in proportion to a persons age. If intraocular pressure has a parallel relation with blood pressure, it must also increase as a person ages. Clinical investigations were made on 1282 normal people from the ages of 8 to 92, however no increase of intraocular pressure seemed to have accompanied an increase in age.

Maximum-and Minimum-blood pressure and I.O.P. In 472 cases of healty persons, aged 8 to 80 and 177 cases of patients who had abnormally high or low blood pressure (121 cases of essential hypertension, 22 cases of renal hypertension, 23 cases of heart disease and 10 cases of hypotension), the relation between blood pressure at maximum and minimum points and I.O.P. was examined clinically and statistically. In both

groups, no significant relationships between blood pressure and I.O.P. could be found.

From the above clinical and statistical observations, I.O.P. seems to have little relation to general blood pressure, but seems to be independently controlled in maintaining the phssiological value.

Relations between the pressure of a circulating fluid in the head and I.O.P[7]. For the purpose of clarifying, experimentally, the relations between general blood pressure and I.O.P. under simple conditions, an artificial circulation experiment using rabbits was made. Irrigation, with a normal salin solution, through the bilateral carotid arteries undertaken with the different pressure and I.O.P. variations being recorded by manometry.

In the rabbits, which died half-way through the circulation experiment, the I.O.P. rose gradually, together with the increase of fluid pressure, and then maintained a maximum value at a certain level.

In living rabbits, however, the I.O.P. temporarily increased following a rise in fluid pressure, and then after a while decreased and it seemed to have a tendency to return to its initial value. A variation of I.O.P. following the pressure-variation of the circulating fluid is less intensive in a living rabbit than in a dead one.

This phenomenon suggests that in living rabbits there is a certain physiological autonomic eye pressure adjustment function which adjusts I.O.P. to any variation in the general blood pressure.

2) The influence of eyeball-compression on I.O.P[8].

Using rabbits anesthetized with Urethan, the eyeballs were compressed by an ophthalmo-dinamometer, with twenty-two gms pressure being exerted upon the cornea.

The variations of I.O.P. were then recorded by manometry. A sudden increase of I.O.P. occured just after the compression of the eyeball, and this was followed by a gradual decrease in pressure which continued for 5 to 10 minutes (an average of 6.6 minutes) until finally the I.O.P. returned to its initial level. At the moment of the removal of compression, a sudden decrease of I.O.P. occurred. However the pressure gradully returned to normal in from 4 to 10 minutes. (an average of 7.35 minutes). This phenomenon suggests that the automatic eye pressure adjustment function is in the eye itself.

3) Consensual ophthalmotonic reaction

To further examine autonomic eye pressure adjustment functions, the following experiment was made, again using rabbits[9]. The I.O.P. of one eye was artificially rasised (60-80 mmHg) or lowered (10 mmHg) and then the I.O.P. of the other eye and the blood pressure of the carotid artery were recorded simultaneously by manometry. If the I.O.P. was raised artificially in one eye, a lowering of the I.O.P. was found in the other eye. If the I.O.P. in one eye was lowerd artificially, a raising of the I.O.P. in the other eye was demonstrated. Hence, it is presumable that there is a ceartain function preventing the change of I.O.P., when an abnormal variation of

I.O.P. happens.

4) Phasic variation of I.O.P.

It is a well known fact that I.O.P. dose not always have a constant value and that there is some physiological variation in it. The phasic variation of a healthy eye, however, is very small in value. However in a glaucomatous eye, the diurnal variation is considerable and sometimes exceeds 50 mmHg.

The I.O.P. of 62 healthy eyes, of 44 eyes with simple glaucoma, and of 22 eyes with congestive glaucoma were measured 6 times daily with a 4 hour interval between each measurement. Abnormal diurnal variation of I.O.P. exceeding 5 mm.Hg, occured in only 4.5% of the normal eyes, but in 86.4% of the eyes with simple glaucoma and in 91.7% with congestive glaucoma.

The above seems to indicate that under normal healthy conditions there seems to exist a physiological function which constantly maintains the I.O.P. at a certain level disregarding the external influences of the body.

5) Provocative tests.

Several provocative tests were employed at our clinic[10]. For instance, in the lability test, the difference between I.O.P. after and before this test was 1.5 to 9.5 mm.Hg (an Average of 4.6 mm.Hg) in 20 healthy eyes, and from 2 to 58 mm.Hg (an Average of 11.9 mm.Hg) in 45 eyes with primary glaucoma, This fact indicates that the capacity for resistance to an extra load in a healthy eye is greater than that in a glaucomatous eye.

Conclusion

The existence of autonomic eye pressure adjustment functions was demonstrated in various ways, both clinically and experimentally. It is possible to consider that in normal condition, I.O.P. seems to be controlled autonomically irrespective of the internal or external influences of the body.

The author calls such a phenomenon "autonomic eye pressure adjustment function".

The mechanism of this physiological function will be reported on in following articles.

II. Relationship between diencephalon and intraocular pressure.

It is well known that in a diencephalon there are many autonomic centers which regulate numerous important functions. Therefore, in our search for the autonomic eye pressure adjustment centers, diencephalon must be investigated first of all. In the past, Magitot[11], Elwyn[12], Thiel[13], Schmerl and Steinberg[14], and others have suggested that the eye pressure center might exist in the diencephalon. More recently, Kurotsu[15], Nagai[16], Sallmann and Löwenstein[17], have provided evidences of centrally elicited changes in the eye pressure.

By the stimulation of diencephalon under various conditions, the author has investigated the influences of the stimuli on the intraocular pressure and on the other

hand, pursued the variations of the eye pressure in the cases of the diencephalo-hypophyseal diseases. According to the results thus obtained, the relationship between the diencephalon and the intraocular pressure has been studied.

Methods and Results.

The experiments were carried out with the use of the method devised by Prof. Kurotzu. Adult rabbits were used, and as for the sites of stimulation, Prof. Kurotsu's so-called b-sympathetic area(the ventromedial hypothalmic nucleus) and c-parasympathetic area (the lateral hypothalamic nucleus) were selected.

The variations by stimuli in intraocular pressure, blood pressure, the width of the lid fissures, the behavior pattern of pupils, and nictitating membrane were recorded simultaneously.

Finally, after the experiments, the author confirmed whether the proper anatomical points had been stimulated or not by histologic examinations of the serial-section specimens obtained from each animal.

1) The relationship between the stimuli in the diencephalon and the intraocular pressure[10].

The rabbits used in the present experiment were 41 in all, but the ones in which the right anatomical points of the stimulus had been touched numbered only 17. (b-sympathetic area, 6 ; the c-parasympathetic area, 11). The symptoms provoked by electric stimulation varied in proportion to the intensity of the stimulus.

i. Stimulation in the b-sympathetic area. As the responses vary according to the intensity of stimuli these are divided into two, for the weak and the strong stimulations.

Results in the cases of weak stimulation. The intraocular pressure in the majority of cases show an extremely slight fall (0.1-1.0 mm.Hg), while the systemic blood pressure is variegated, some will show a marked rise, the others a marked fall, and still others show a rise followed by a fall. The decreasing curve of the eye pressure begins to fall rather gradually after stimulation, but after the cessation of stimulation it rises slowly and finally reaches the original pressure. No evidence of parallel relationship seems to exist between the eye pressure and the systemic blood pressure, though a slight mydriasis is revealed in all cases.

Results in the cases of strong stimulation. Strong stimulation in the sympathetic area results in a rapid, marked elevation of the eye pressure (1-5 mm.Hg) without exception. As for the systemic blood pressure, however, some cases demonstrate a sudden rise while others show a rise at first, then a temporary drop below the initial pressure. In the cases showing a rise in the eye pressure, all have been found to exhibit symptoms such as exophthalmus, widening of lid fissures, systemic spasm, and a rise of the systemic blood pressure simultaneously. Therefore, a sudden rise of the eye pressure provoked by strong stimulation seems in all likelihood to be a complimentary response to the contraction of the intraorbital smooth muscle and to an elevation of the

systemic blood pressure.

ii. Stimulation in the c-parasympathetic area.

Results in the cases of weak stimulation. Some are occasionally found to show no change of the eye pressure but the most of them reveal a moderate rise(0.1–1.5 mm.Hg). As for the systemic blood pressure, on the other hand, there are various cases: some showing a rise while others a fall, and still others a rise then a fall. As for the reactions of pupils, the majority of the cases show miosis but there are some that reveal no change; and as a rule, no other changes can be seen.

Results in the cases of strong stimulation. The eye pressure invariably rises rapidly and markedly (2-8 mm.Hg); and the systemic blood pressure in some cases rises at first than falls later, while in some it only keeps on rising. Pulils in general reveal miosis, but in rare instances, mydriasis or transient miosis followed by mydriasis. The widening of lid fissures and the systemic spasm have been observed in all the cases. From this fact the rise in the eye pressure observed in the strong stimulation may be considered as being intimately correlated with the orbital and the systemic behavioural changes.

From these results, it may be said that in the stimulation of the sympathetic area the eye pressure generally falls, while in that of the parasympathetic area it invariably rises, excepting the influences of the contraction of the orbital smooth muscles, the systemic spasm, and the rise of the systemic blood pressure, all occurring simultaneously when the diencephalon is stimulated. No evidence of parallel relationship between the changes of eye pressure and those of systemic blood pressure can be found.

iii. Relationship between the stimulation of the diencephalon and fluorescein inflow-rate in the anterior chamber.

In order to investigate the production of aqueous humor, the rate of the inflow into the anterior chamber, of the fluorescein previously venously has been examined by Amsler-Huber's method. As the results, it has been observed that the rate of the inflow of fluoresein into the anterior chamber was inhibited by the stimulation of the sympathetic area, whereas in the cases of the stimulation in the parasympathetic area it was accelerated. This fact is suggestive of the nervous regulating mechanisms of the aqueous humor production, inhibition by sympathetic stimulus but the acceleration by the parasympathetic one.

iv. Relationship between the unilateral stimulation in the diencephalon and the pressure of the eye on the unstimulated side.

The changes of the eye pressure and the pupillary size on the stimulated side in the case of unilateral stimulation of the diencephalon have been compared with the respective changes of those on the unstimulated side. Even in the eye on the unstimulated side, the similar changes are revealed, as those in the eye on the stimulated side, though the degree of these changes seems to be slight.

2) The eye pressure changes observed in the diencephalon-cauterized rabbits[10].

If the so-called autonomic eye pressure adjustment center does really exist, it is reasonable to assume that some disturbances of eye pressure should be expected when that center is destroyed. Upon this assumption, the following experiment has been conducted.

Normal adult rabbits were divided into 3 groups and the first group was subjected to the unilateral cauterization of the diencephalon, the second group to the unilateral cauterization of the diencephalon as well as the ligation of the vortex vein, and the third group to the cauterizations of the diencephalon on one side and of the angle of the anterior chamber on the same side.

The results of the first group. The phasic variations of the eye pressure on both the cauterized and the uncauterized sides were generally greater compared with those before the cauterization and also the difference of the eye pressures between both eyes of the same rabbit as compared with the difference of those before the cauterization was greater. The maximum eye pressure, however, was 27.3 mmHg and there was none that exceeded 30 mm.Hg.

The results of the second groups. As a preliminary experiment, the changes in the intraocular pressure of normal rabbits were investigated by the ligation of vortex veins. The eye pressure had shown a transient rise immediately after the ligation, but 24 hours later it fell markedly below the normal level. Subsequently it again rose gradually and 9 days after the ligation it returned approximately to the initial pressure; and ever since the animals have been maintaining the normal pressure. With those rabbits whose diencephalon had been cauterized, the fluctuations of the eye pressures were greater, and the difference of the eye pressures between both eyes of the same rabbit were also greater. In one of these cases, its eye pressure was above 31 mm.Hg, for several days.

The results of the third group. As a preliminary experiment, the pressure by electric cauterization of the angle of the anterior chamber of 7 rabbits were investigated. The eye pressure showed a marked but transient fall after the cauterization, but on or about the 12the day, the pressure was found to have recovered to the initial level. None, however, showed rise in the eye pressure. On the contrary, in the rabbits with the cauterized diencephalon, the variations of the eye pressure after the cauterization of their angles became greater; and the author encountered one whose eye pressure reached even above 31 mm.Hg.

From these results, it seems that the phasic variation of I.O.P. becomes greater when the diencephalon is destroyed, and furthermore, that when the local lesions such as the ligation of the vortex vein or the cauterization of the angle of the anterior chamber is given, not only variations of the eye pressure become greater but also there is a tencency to accelerate abnormally the rise of the pressure.

3) Influences of philopon (Methamphetamine hydrochloride) and phenobital (phenobarbitalum solubile) upon the eye pressure of the normal individual[18].

Jeansch and Thiel[13] reported that the eye pressure of the patient with glaucoma had been found to fall by administering the sedatives for the diencephalon such as Luminal or Ergotamine, but to rise by giving an excitatory drug, Pervitin. Heim[19], Wiener[20], Glavan[21], Popvici[22], Gifford[23], and Abadii[24] agreed to this report, but recently Agarwal[25] has presented a contradictory opinion.

The author injected Philopon and Phenobital subcutaneously into normal persons and obtained the following results. Namely, with Phenovital, a drug acting on the diencephalon sedatively, a lowering of the eye pressure, though slight, has been observed; but with Philopon, an excitatory drug, the rise in the eye pressure has been definitely recognized. In other words even in the normal person, just as well as in the patients with glaucoma, it has proven that the drug acting sedatively on the diencephalon lowers the eye pressure while the excitatory drug raises it.

4) Diurunal variations of eye pressure and the results of provocative tests in the patients with pituitary tumor[26].

If an assumption is made that the diencephalo-hypophyseal system is involved in the regulation of eye pressure, then it naturally follows that autonomic adjustment functions of the eye pressure would be in some way affected by the presence of tumor or inflammations in the vicinity of the pituitary body.

There are a considerable number of works on the relationships between the eye pressure and the pituitary body. (Imre[27], Jeandelize[28], Yamashita[29], Szily[39]). The author has investigated the diurnal variations of the eye pressure and the reactions to the various provocative tests, in the 6 patients with pituitary tumor and 2 patients with arachnoiditis and then has come upon an interseting finding in regard to the relationship between the two.

The restults are as follows: the 10 eyes showed the diurnal variations of the eye pressure above 5 mmHg (max. 29 mmHg); one of them had the absolute value of the eye pressure of more than 30 mmHg; and in thh provocative tests, the majority of cases gave positive results.

Therefore, it will be able to conclude that eye pressure adjustment function seems to be perhaps impaired in patients with diencephalo-hypophyseal diseases.

Such functional disturbances recovered somewhat by extirpation of the tumors.

5) Cases of diencephalo-hypophyseal glaucoma.

If there is an eye pressure adjustment center in the diencephalo-hypophyseal system, then in the case of an impairment of the diencephalo-hypophyseal system, glaucoma should necessarily accompany. Zondek[31], in his exhaustive examinations of the 22 cases with primary glaucoma, has found the impairment of various degrees in the diencephalo-hypophyseal system in the 16 cases. The author[32] has also observed two cases with pituitary tumor accompanied by simple glaucoma.

Conclusion

The author has carried out the investigation from various angles on the relationship

between the function of diencephalon and the eye pressure, and has found that all the evidences in the investigations point to a quite important rôle being played by the diencephalon in the regulation of the eye pressure.

Today it is a common physio-anatomical knowledge that the functions such as respiration, pulsation, blood pressure, and digestive actions which are essential for the maintenance of life, all possessing autonomy, are performed and regulated by the centers existing in the diencephalon. Now, the eye pressure, having such an important ralationship to the visual functions, can not possibly be a lone exception. From these, therefore, it may be concluded that at least an autonomic center of the eye pressure exists in the diencephalon.

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VARIATIONS IN OCULAR TENSION AND BIOMICROSCOPIC ASPECTS OF AQUEOUS VEINS

Significance of Aqueous Veins in the Glaucoma Problem

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The detection of the aqueous veins by K.W. Ascher in 1914 has demonstrated the continuous flow of aqueous humour. It has enabled us to observe directly the aqueous outflow, details of which have been previously obscure, and, certainly, has opened a new field of research concerning the problems of the physiology and pathology of intraocular pressure. Interest in the aqueous veins has grown; during the last decade numerous splendid investigations have been published. At the present time, however, the role of the aqueous veins in the physiology and pathology of intraocular pressure is not yet fully elucidated. Intending to evaluate the significance of the aqueous veins in the glaucoma problem, the author has, for several years, made clinical observations, under various conditions, on the aqueous veins in normal and in glaucomatous eyes. The results are summerized in this paper.

Designation of Aqueous and Sanguineous Contents of the Aqueous Veins.

It is obvious that the amount of aqueous outflow through the aqueous veins is increased when the clear stream in the aqueous veins widens, and it is decreased when the sanguineous stream widens. However, no correct and accurate method of estimating the amount of aqueous outflow through the aqueous veins has been established so far. Because the principal purpose of my own study was to observe, whether the significant correlation might be demonstrated or not between variations in the contents of the aqueous veins and those in the ocular tension, I intended to describe the pattern of the variations in the contents of the aqueous veins, if possible, plotting it on a

Fig. 1 Scale for designation of the contents of the aqueous vein.

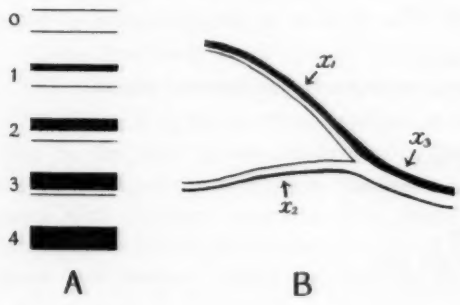
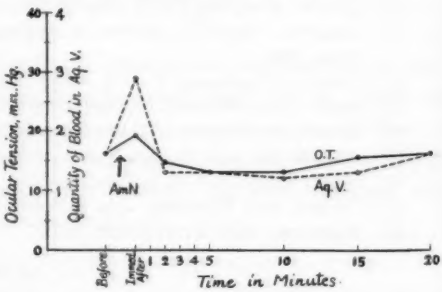


Fig. 2 (Normal O.D., a male aged 40 yrs.) Variations in ocular tension and in contents of an aqueous vein in response to the inspiration of amyl nitrite



graph. I devised five scales for the designation of the quantities of blood mixed in the contents of the aqueous veins (Fig. 1A): A purely clear aqueous vein is designated as "0"; when the width of the blood column occupies one-fourth of the aqueous vein, designated as "1"; when a half, as „2"; when three-fourths, as "3"; pure blood stream, as "4". Accordingly, the smaller the figure, presumably the greater the quantity of aqueous flow through the aqueous vein.

Of course, this measurement is not absolutely correct and accurate, rather fairly erroneous. I used, therefore, the arithmetical mean of figures obtained at several points, in most cases three points, of the same aqueous vein, including its recipient vein (Fig. 1B).

Mechanical Interferences with Aqueous Elimination through Aqueous Veins.

Electro-Coagulation of the Bulbar Conjunctiva All Around the Corneal Limbus. In four normal rabbit eyes one to 1.5 mm. of the bulbar conjunctiva was electro-coagulated superficially all around the corneal limbus in order to obstruct the aqueous flow through the episcleral vessels. In all the eyes the ocular tension was raised immediately after the intervention, then dropped to or below the initial level after about five hours, and showed no noticeable rise during the following period for about twently seven hours. If we assume that no other aqueous-drainage pathway than the canal-of-Schlemm-aqueous-vein unit exists, then in these instances where all the superficial vessels were destroyed, the aqueous humour was unable to empty into the collateral vssels. Therefore it is reasonable to assume that the variations which occur in ocular tension are not induced by the obstruction of aqueous drainage through the episcleral vessels.

Ligation of the Jugular Veins. The ligation of the jugular veins may increase the resistance to aqueous outflow, causing a rise in the episcleral venous pressure, and may result in interference with the aqueous elimintation through the episcleral vessels. With rabbits I ligated the jugular veins of both sides. No discernible rise in ocular tension was found during the observation period of one to two hours.

Lability Test and Backflow of Blood in the Aqueous Veins. A stoppage of the flow of clear fluid or a backflow of blood in the aqueous veins occurs in human eyes at the moment when the compression of the jugular veins with the rubber cuff of a sphygmomanometer settled all around the neck reaches a definite level (Kishimoto (3), Weinstein (4), Thomassen and Leydhecker (5), Kleinert (6)). It is obviously accepted that the compression of the jugular veins causes a rise in the episcleral venous pressure (Hiroishi (7), Thomassen and Leydhecker (5)). If the intravascular pressure of the episcleral veins is elevated to the same level which governs the aqueous flow in the aqueous veins, a stop of aqueous flow in the aqueous veins may occur; if the episcleral venous pressure rises, however slightly, above the level of the pressure in the aqueous

veins, a backflow of blood may occur. From these criteria it is assumed that, when a backflow of blood can be easily elicited, in other words by a lower level of the jugular compression, the elimination of aqueous humour through the aqueous veins may be less vigrous than in the event where a higher level of compression is required. The question arises whether a positive lability test would occur in eyes which require a low jugular compression.

On glaucomatous eyes I studied the levels of the jugular compression which were required to cause backflow in the aqueous veins, in comparison with a positive or negative response to the lability test. Of 29 glaucomatous eyes examined (20 with chronic simple glaucoma, 9 with chronic congestive glaucoma), the lability test was positive in 15 eyes, and negative in 14 eyes. Fifteen aqueous veins were found int he lability-test-positive eyes and 17 aqueous veins in the negative eyes. The relationship obtained between the response to the lability test and the jugular-pressure level which was required to cause a backflow was:

Level of Jugular Compression (mm.Hg.)	No. of Aqueous veins found in Lab.-test-pos. eye	Lab.-test-neg. eye
29 or less	4	4
30 to 45	6	7
46 or more	5	6
Total	15	17
Mean value	42.5 mm.Hg.	33.3 mm.Hg.

These results demonstrate that the labbility test was not necessarily positive in those eyes where aqueous veins required lower levels of jugular compression to cause a backflow; that rather the mean value for the lability-test positive eyes was higher than that for the negative eyes; but a significant difference was not proved statistically between them. Furthermore, the ranges of the levels of compression and the incidences of the aqueous veins in each pressure level were almost identical in lability-test-positive or negativ eyes. Therefore, it may be concluded that the vigour of aqueous flow through the aqueous vein has no causative relation to the amount of rise in ocular tension produced by the lability test.

Variations in the Contents of Aqueous Veins and Those in Ocular Tension.

Dark-Room Test. Twenty six glaucomatous eyes (17 with chronic simple glaucoma, 8 with chronic congestive glaucoma, one with secondary glaucoma)were examined. The patient were kept in the darkness for one hour and then the observations were made in regard to whether positive or negative responses to dark-room test might correspond, respectively, to a decrease or an increase in the clear content of the aqueous veins.

As illustrated in Table 1, the tests were positive only in such eyes in which the darkness had induced a decrease in the clear content. The average values of the amount of rise in ocular tension increased in the following order: (1) the eyes with a diminution of the clear content in the aqueous veins, (2) the eyes with no change, (3)

Table 1 Relationship Between the Changes in the Content of the Aqueous Veins and the Responses to Dark-Room Test in Glaucomatous Eyes

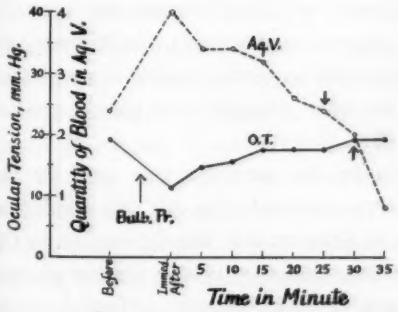
Changes in Clear Content	Total Eyes	Dark-Room Test		Average Rise in Ocular Tension mmHg.
		Positive	Negative	
Increase	3	0	3	+ 1.42
No Change	8	0	8	+ 2.61
Decrease	15	6	9	+ 5.13
Total	26	6 (23.1%)	20 (76.9%)	

The sign+ indicates the rise in ocular tension.

the eyes with an augmentation of the clear content. Of 15 eyes showing a diminution of the clear content, however, 9 eyes had a negative response; among those 9 eyes there was even one eye in which the ocular tension fell considerably (9.5 mmHg.). In all three eyes which showed augmentation of the clear content in response to darkness, some, but not much rise in ocular tension was observed. In consequence, it may be assumed that the diminution or augmentation of the clear content of the aqueous veins has no causative correlation with the rise in ocular tension in response to the dark-room test.

Inspiration of Amyl Nitrite. The patient inspired some drops of amyl nitrite; the ocular tension and the contents of the aqueous and recipient veins were repeatedly measured, first at short intervals of 30 to 60 seconds, and then at intervals of 5 minutes for a period of about 20 minutes. Fourteen normal and 20 glaucomatous eyes (15 with chronic simple glaucoma, 5 with chronic congestive glaucoma) were examined.

Fig. 3 (Chronic simple glancoma O.D., a female aged 53 yrs.) Variations in contents of an aqueous vein and in ocular tension caused by the bulbar pressure test of Suda. Arrows indicate the moment when they returned to their initial state.



Plotting the measures taken from the ocular tension and the contents of the aqueous veins in the same chart (an example is shown in Fig. 2), the curves of the ocular tension were compared with those of the contents of the aqueous veins. There appears to be a significant correlation between them, when a rise in ocular tension coincides with an increase in the blood content of the aqueous veins and vice versa. The results on 14 normal and 20 glaucomatous eyes are:

	No. of Eyes	
	Normal	Glaucomatous
Significant Correlation	6 (42.9%)	7 (35%)
Insiginificant Correlation	8 (57.1%)	13 (65%)
Total	14	20

In both normal and glaucomatous eyes, more than one half of the eyes displayed no significant correlation. These results suggest that the changes in the quantity of aqueous flow through the aqueous veins does not necessarily govern the variations in ocular tension caused by the inhalation of amyl nitrite.

Bulbar Pressure Test of Suda. External pressure exerted on the eye globe forces the expression of aqueous humour and expels the blood out of the inner eye. Immediately after the pressure release, therefore, the ocular tension is remarkably lowered, and then followed by a gradual return to its initial level. Assuming that the aqueous veins are the unique drainage pathways for aqueous humour out of the eye, the behaviour of the aqueous veins which was observed during the phase when ocular tension returned to its original level may indicate the way in which the aqueous formation and outflow reaches its original equilibrium.

The bulbar pressure test of Suda consists of the application of sustained pressure at 50 gm. for 10 minutes by means of the ophthalmodyamometer of Baillart toward the center of the globe at the site of the insertion of the rectus muscle. Tonometric readings are taken just before the application of pressure and immediately after its release, and then progressive changes in tonometric reading back to the initial level are repeatedly measured; the so-called ocular-tension-lowering percentage (Suda) is calculated by the formula:

$$\frac{\text{Initial tension—Tension immediately after pressure release}}{\text{Initial tension}} \times 100.$$

In my personal observations, following the pressure release, progressive changes in the contents of the aqueous vein were repeately measured simulataneously with those in ocular tension as well as the time taken by the aqueous vein to return to its original state.

These observation were performed on 10 normal and 16 glaucomatous eyes (13 with chronic simple glaucoma, 3 with chronic congestive glaucoma). In the aqueous veins of all the eyes studied, a remarkable augmentation of the sanguineous content was consistently found immediately after the pressure release, and then a gradual diminution until it returned to its original state (Fig. 3).

First the relationship between the time taken by the aqueous vein and by the ocular tension to return to their initial states was observed (Fig. 4). No significant correlation was found. Special notice was taken to determine if the time taken by the aqueous vein was in inverse proportion to the time taken by ocular tension since a delayed aqueous outflow might cause a rapid return of ocular tension. Next, as illus-

Fig. 4 Relationship between the times taken by the aqueous vein and by ocular tension to return to their initial state.

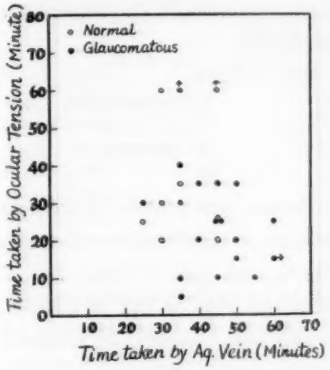


Fig. 5 Relationship between the ocular-tension-lowering percentage (Suda) and the time taken by the aqueous vein to return to its initial state.

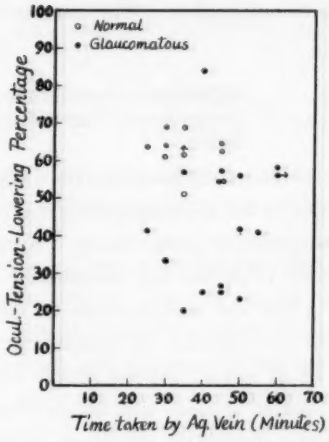
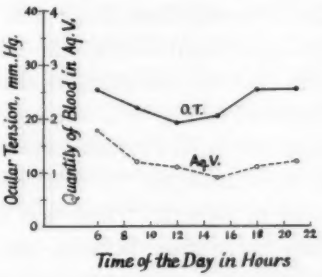


Fig. 6 (Chronic simple glaucoma O.D., a female aged 65 yrs.) Spontaneous diurnal phasic variations in ocular tension and in contents of the aqueous vein, showing the significant correlation between them



trated in Fig. 5, with regard to the relationship between the ocular-tension-lowering percentage(Suda)and the time taken by the aqueous vein to return to its original appearance, no significant correlation was found, i.e. the aqueous vein of the eye with large ocular-tension-lowering percentage—where the amount of ocular tension to be recovered was great in order to reach its initial level—did not necessarily take a longer time than the eye with small ocular-tension-lowering percentage. Hence it is suggested that, after the release of bulbar pressure, the variations in the contents of aqueous veins are of little significance in regard to the recovery of the lowered ocular tension.

Administration of Diamox. On 11 normal and 24 glaucomatous eyes(17 with chronic simple glaucoma, 6 with chronic congestive glacoma, one with secondary glaucoma), I studied the changes in the contents of the aqueous veins in comparison with the modifications of the ocular-tension curves after an administration of Diamox. A lowering of the ocular tension and a diminution of its diurnal oscillation were produced in the majority of the glaucomatous eyes, whereas only a little effect was produced in the normal eyes, as pointed out by many investigators, on the one hand. On the other

hand, examination of the aqueous veins revealed the variability of response to the drug. Comparing the curves of ocular tension with those of the blood content of the aqueous vein, a correlation was regarded as significant, provided that the falling phase of ocular tension and the decreasing phase of blood content of the aqueous vein corresponed to each other. The results were the following:

	No. of Eyes	
	Normal	Glaucomatous
Significant Correlation	7 (63.6%)	9 (37.5%)
Insignificant Correlation	4 (36.4%)	15 (62.5%)
Total	11	24

The incidence of the eyes with a significant correlation was greater in the normal eyes and smaller in the glaucomatous eyes, but the incidences of significance and insignificance proved statistically insignificant. From these criteria, the tide of blood which entered the aqueous veins did not necessarily correlate with the rise or fall of ocular tension, suggesting that the modifications of the ocular-tension curve caused by Diamox did not depend on the quantity of aqueous flow through the aqueous veins.

The Spont aneous Diurnal Phasic Vaaiations in Ocular Tension and Those in the Aqueous Veins. Eleven normal and 30 glaucomatous eyes (19 with chronic simple glaucoma, 9 with chronic congestive glaucoma, 2 with secondary glaucoma) were examined. Slit-lamp observations of the aqueous veins and tonometries were performed every two to three hours during one to two days. In comparing the curve of ocular tension with the curve of blood content of the aqueous vein, it was difficult, in the normal eyes, to decide exactly whether or not there might be corresponding variations between them since little oscillation of ocular tension was found. Whereas, among the glaucomatous eyes, the cases were found where two curves had a significant correlation (the corresponding oscillation) as illustrated in Fig. 6, as well as the cases where two curves did not have asignificant correlation(Fig. 7). The results are shown in Table 2. There was no significant correlation between the ocular tension and contents of the aqueons veins in more than half the number of glaucomatous eyes. Especially in regarding the eyes with chronic simple glaucoma a significant correlation was found only in 6 out of 19 eyes. Therefore, it is doubtful that the variations in the contents of the aqueous veins have a causative correlation to the diurnal oscillations of ocular tension, as postulated by Thomassen, and Duke-Elder (16).

Fig. 7 (Chronic simple glaucoma O.S., aged 44 yrs.) Spontaneous diurnal phasic variations in ocular tension and in contents of the aqneous vein, showing the insignificant correlation.

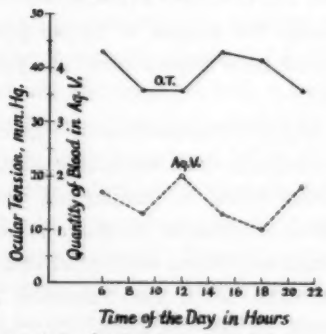


Table 2 Relationship Between the Spontaneous Diurnal Phasic Variations in Ocular Tension and in Contents of the Aquous Vein in Glaucomatous Eyes (Figures indicate No. of eyes.)

	Chronic Simple Glaucoma	Chronic Congestive Glaucoma	Secondary Glaucoma	Total
Close Significant Correlation	1	1		2 (6.7%)
Slight Significant Correlation	5	3		8 (26.7%) } 10 (33.3%)
Insignificant Correlation	13	5	2	20 (66.7%)
Total	19	9	2	30

The Diurnal Phasic Variations in Ocular Tension and Those in the Jugular-Pressure Level Which are Needed to Cause Backflow in the Aqueous Veins. The rise in the episcleral venous pressure can interfere with the outflow of aqueous humour through the episcleral vessels. Then the flow of aqueous humour through the aqueous veins may become less vigorous and can be obstructed by the lower level of jugular compression. Therefore, it may legitimately be supposed, that the level of jugular compression, which is needed to cause backflow in the aqueous vein can be used as an indirect index indicating the degree of vigour of aqueous flow through the aqueous vein.

On 9 normal and 24 glaucomatous eyes (16 with chronic simple glaucoma, 6 with chronic congestive glaucoma, 2 with secondary glaucoma), I made a comparative study of the diurnal changes in ocular tension and those in the levels of jugular compression. The author believes that there is significant correlation between them when the rising phase of ocular tension corresponds to the lowering of the level of jugular compression. In the majority of the normal eyes the judgement was difficult because of minimum oscillations in both the ocular tension and the jugular-pressure level, and no eye showed a significant correlation. The majority of the glaucomatous eyes showed

Teble 3 Relationship Between the Diurnal Phasic Variations in Ocular Tension and in Jugular-Pressure Level Needed to Cause Backflow in Aqueous Vein in Glsucomatous Eyes. (Figures indicate No. of eyes.)

	Chronic Simple Glaucoma	Chronic Congestive Glaucoma	Secondary Glaucoma	Total
Significant Correlation	4	3		7 (29.2%)
Insignificant Correlation	10	3	2	15 (62.5%)
Difficult to Judge	2			2 (8.3%)
Total	16	6	2	24

either a significant correlation or an insignificant relation. As illustrated in Table 3, however, the incidence of insignificant correlation was remarkably greater. From this viewpoint it is suggested that the vigour of aqueous flow through the aqueous veins may play little causative role in the changes in or in the regulation of ocular tension.

The Diurnal Variations in Tonographic Values and Those in the Appearance of the Aqueous Veins. Using Mueller's electronic tonometer, I studied the diurnal changes in tonographic measurements on 2 normal and 10 glaucomatous eyes (6 with chronic simple glaucoma, 3 with chronic congestive glaucoma, one with secondary glaucoma). The changes in the value "R" and "F" were compared in each eye with those in the sanguineous content of the aqueous veins. Theoretically the blood content of the aqueous vein must be in proportion to the value R ond in inverse proportion to the value F, and if so, it might be considered that there is a significant correlation between them. The results were: Of 10 glaucomatous eyes,in only 2 eyes the contents of the aqueous vein showed a significant correlation to R, and in only 3 eyes to F. In no normal eye was a significant correlation found. Although a reliable conclusion cannot be drawn on the basis of a limited number of observations, the changes in R or F of tonographic measurement seem to have no necessarily causative relation to the changes in the contents of the aqueous vein.

Difference between Aqueous Veins of Normal and Glaucomatous Eyes.

Concerning the differences between the aqueous veins of normal eyes and those of glaucomatous eyes, it has been emphasized that, in regard to the glass-rod phenomenon (Ascher), the aqueousand recipient veins of glaucomatous eyes almost always show the blood-influx phenomenon; whereas those of normal eyes show either the aqeous-influx phenomenonor the blood-influx phenomenon. According to Goldmann, the amounts of external bulbar pressure which are needed to widen the diameter of the clear stream in anaqueous vein are generally low for normal eyes, whereas glaucomatous eyes require higher readings so long as the ocular tension is elevated.

Ascher (9) stated that aqueous veins were less frequent in eyes with chronic simple glaucoma; that they were, on average, smaller in glaucomatous eyes; that their current was less vigorous, and that it was more difficult to find aqueous veins in eyes with congestive glaucoma and in eyes with secondary glaucoma. In my personal observations, aqueous veins occurred in almost all the normal eyes, whereas their incidence in eyes with chronic simple glaucoma was 88.5% (23 eyes of 26 eyes) and in eyes with chronic congestive glaucoma was 81.5% (9 eyes of 11 eyes). Although the incidences in glaucomatous eyes seem to be somewhat smaller than in normal eyes, only wide and clearly visible aqueous and recipient veins suitable for the various investigations mentioned above are taken into account. Therefore their incidence in glaucomatous eyes may become greater and may be little different from the incidence in normal eyes, if even thin and scarcely visible ones are counted. The number

of clearly visible aqueous veins in each eye did not differ essentially between normal and glaucomatous eyes when the bulbar conjunctiva did not congest.

As mentioned above, the amount of jugular compression which is needed to cause backflow in an aqueous vein may be used as an indirect index indicating the degree of vigour of aqueous flow through the aqueous vein. I performed this measurement on 72 aqueous veins of 68 normal eyes and on 46 aqueous veins of 43 glaucomatous eyes. The results were as follows:

	Total Aqueous Veins	Level of Jugular Compression (mm.Hg.) 29 or less	30-45	46 or more	Average
Normal	72	18 (25%)	43 (59.7%)	11 (15.3%)	35 mm.Hg.
Glaucomatous	46	11 (23.9%)	22 (47.8%)	13 (28.3%)	37.6 mm.Hg.

The range and the average value were almost identical in normal and in glaucomatous eyes; so were the distribution of the incidence of aqueous veins in each level of jugular compression.

The behaviour of aqueous veins in response to inspiration of amyl nitrite were quite similar in normal and in glaucomatous eyes in their pattern and chronological course.

From my personal observations, it is reasonable to conclude that the aqueous veins of normal and of glaucomatous eyes do not substantially differ as regards their quality as well as their quantity.

Histological Evidence of the Drainage Pathway of the Aqueous Humour.

According to the suggestion of Schreck (26), I used an isotonic iso-ionic solution of iron citrate as the test substance to be introduced into the anterior chamber. Twenty two normal rabbit eyes were used. The solution was injected into the anterior chamber under the pressure identical with or considerably higher (at 40 to 50 mmHg.) than the intraocular pressure. The eyeballs were enucleated within 8 to 20 minutes after the completion of the injection; sectioned in serial specimens. Each specimen underwent the prussian-blue reaction and the blue tint was examined microscopically. Four human eyes to be enucleated owing to malignant tumours and severe chronic intraocular inflammation were also used. In these the aqueous humour was replaced by the test solution before enucleation.

The findings in the rabbit eyes and the human eyes showed marked similarity. The principal findings can be summerized as follows: The blue tint was not recognized in the posterior chamber and in the vitreous body. It was particularly intense at the chamber angle inclusive of the corneoscleral trabeculae, and was recognized in the canal of Schlemm, in the lumina of the intrascleral venous plexus and of the episcleral veins and, in some specimens, also in the lumina of the vessels near the insertion of the rectus muscle. Furthermore the test substance found its way into the lumina of vessels of the iris and into the outermost layer of the ciliary body, thence into

the lumina of vessels of the ciliary body and of the choroidal vessels and, finally, into the lumina of the vortex veins.

The canal-of-Schlemm-aqueous-vein unit for aqueous drainage is well established in my personal findings also. In part, however, they contain something worthy of discussion.

Asayama, I (27), and Akagi, Ojima and Kurose (28) found that the dye injected into the anterior chamber left the vortex vein in living rabbit eyes; Gifford (29), and Benoit (30) obtained histologically identical results. The aqueous-elimination pathway through the outermost layer of the ciliary body in a posterior direction has been pointed out by several authors(Gerbrandy(31), Weekers, L.(32), Nakajima, Ch.(33), Takahashi, H. (34), Mikuchi (35), Go (36), Morii). Ashton (27), and Takahashi, M. (37) proved the anastomoses between the collector channels of the canal of Schlemm and the venous plexus of the ciliary body. Dvorak-Theobald (38), in her recent anatomical studies on the canal of Schlemm, has confirmed that the collector channels of the canal join the deep intrascleral plexus, thence some of the branches from the deep intrascleral plexus enter the ciliary body presumably to join the vortex veins.

In reviewing my personal findings and those of other investigators, it should be emphasized that there is surely another drainage system which leads finally to the vortex veins, in addition to the canal-of-schlemm-aqeous-vein system.

Conclusion

A consecutive review of the findings mentioned above indicates, that changes of a significant amount in ocular tension cannot be produced by means of mechanical interferences with aqueous drainage through the aqueous veins; that variations in ocular tension, either spontaneous or contrived, would not depend upon the changes in the quantity of aqueous flow through the aqueous veins which are, however, reflected in the tide of blood content of the aqueous veins. Therefore it is most reasonable to suppose that the role of the aqueous veins may be of little significance in problems of the physiology and pathology of ocular tension.

Moreover, the aqueous veins of glaucomatous eyes do not differ essentially from those of normal eyes as regards their quality and quantity. The canal-of-Schlemm-aqueous-vein unit is not the unique drainage system for the aqueous humour, but there is, to be sure, another effective system leading finally to the vortex veins. Consequently the significance of the aqueous veins in the glaucoma problem may be of little importance. Further studies might bring more convincing information in the future.

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ON THE CHOLINE SUBSTANCE OF THE RETINA

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Choline and acetylcholine have recently been emphasized as the component substance of the retina. They have the important role of conducting the impulse in the layers of the retina except that of the visual cells and in relationship with the visual substance which probably is isolated from phospholipid by light adaptation and also on the study of the process of sensitization in the visual cell.

In 1929 choline was found histochemically by Heiji Hirose. He put a piece of tissue in the saturated solution of hydrargyrum bichloratum, making complex salt of the choline in the tissue and hydrargyrum bichloratum; in dissoluting that by hydrogen sulphide he obtained a black precipitate of mercury sulphide. Namely he proved that

the fine black granules can be considered as equivalence of choline and believed that the so called choline granule was free choline. Nakajima, Yasuma and Fujiu agree with him, but Yamamoto thinks it consists of acetylcholine, lecithin and fatty acid beside choline.

Distribution of the choline substance in the retina is just about the same in various animals. There is most of the choline substance in the layer of visual cells particularly in the outer segment of these cells in frog, chicken, rabbit and rat. There is more choline substance in the light adapted retina than in the dark adarted one and it also is dense in the internal and external reticular layers and less in the internal and external nuclear layers. There are dense granules of the choline substance in the protoplasm of the ganglion cell. The author has found, that there are dense granules in the apex of the external segment of the visual cell of man and more in the cone than in the rod. The choline substance is seen in the inner segment of the visual cell, internal and external reticular layers, nerve fiber layer and ganglion cell in order of content, and it is least in the internal and external nuclear layers and is more in the part coressponding to the foot of the cone.

The author has studied histochemically the following three characters of the choline substance of summer frog, chicken, rubbit and man.

1) Blocking the hydroxyl and amino groups by acetylation
2) Blocking the ethylen group by bromination
3) Blocking free aldehyde by aniline chloride

PAS reaction was done to observe the attitude of the choline substance in these points described above.

1) In one hour acetylation the choline substance of the visual cells extremely decreases but the fine black granules were seen in the external segment of the light adapted retina of rabbit and frog. In 24 hours acetylation the result was the same as that of one hour acetylation. However PAS reaction of the whole layer has already shown negative result in one hour acetylation.

2) In one hour acetylation the fine black granules were not seen completely in the whole layer including the visual cell layer of both light and dark adapted retinas of chicken. The staining of PAS reaction decreases through the whole layer but an oval granule of glycogen was seen in the internal segment of the visual cell of the light and dark adapted retinas. It is negative in the whole layer in more than one hour acetylation.

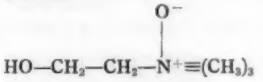
3) In one hour acetylation on the human retina both of the choline staining and PAS reaction were negative in the whole layer. Namely it has been noted that by acetylation one or 24 hours-PAS reaction decreases and the hydroxyl and amino groups of the substance are blocked as far as the PAS reaction is concerned, while the choline substance decreases or disappears parallel to the PAS reaction in the retina of frog, chicken, rabbit and man.

Therefore decrease of staining of choline is not assumed to be unrelated to the PAS reaction. It could not be denied in this experiment that there is an intimate relation between choline and aldehyde.

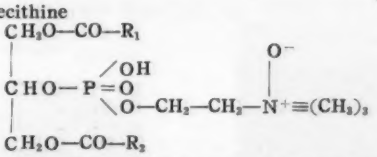
It has been known that there is a certain substance resistant to acetylation which is seen in the external segment of the light adapted retina of the frog and rabbit only, and is seen as a black granule in Hirose's procedure. It is assumed to be some of the choline substance which is increased by light adaptation.

According to the theory of blocking in PAS reaction it is assumed that a phenomena, such as decreasing or disappearing of the stain of choline substance are the results of preventing -OH or $-NH_2$ groups from binding to Hg ion; the choline substance probably contains something which contains -OH or $-NH_2$ groups and causes a mechanism such as prevention of binding. It is thought that choline and lecithine come to be a complex salt of hydrargyrum bichloratum at the point of the -OH group which is bound to N shown below and in acetylation the CH_3CO- group is bound to $O^-—\underset{|}{N}^+\equiv$.

Choline



Lecithine



Therefore it is possible to assume, that these substances are not stained by the choline staining when the mercury becomes free from complex salt. It is the same in the case of acetylcholine also.

The choline substance has been seen only in the outer segment of the visual cell of the light adapted retina of certain animals, when the acetylation was done; it is evident that the choline substance has been increased by light adaptation but it is not clear whether or not some of the choline substance increased by light adaptation remains as result of incomplete blocking or whether it is free choline. However, it is at least sure that the blocking procedure makes the choline substance increase more in the light adapted retina than in the dark adapted one of the frog and rabbit.

In the case of bromination the choline staining is negative in both of the light and dark adapted retinas, but in the PAS reaction it is negative in the visual cell layer and decreases in the reticular cell layer. On the contrary PAS reaction increases in the nuclear cell layer. Lillie has pointed out that decreasing or disappearing of the PAS reaction after bromination is a result of the blocking of CH=CH group and the choline staining also decreases or disappears parallel to the PAS reaction. Theoretically the choline and the acetylcholine, which do not have a CH=CH group, have to remain unchanged without influence of bromination, and they should show positive choline staining. However, it has practically shown a negative result in various retinas, and it is difficult to explain the reason of disappearing of the choline staining by Lillie's hypothesis. The author would assume, that Hg ion is converted to Br ion at

Fig. 1 Choline staining of man's retina

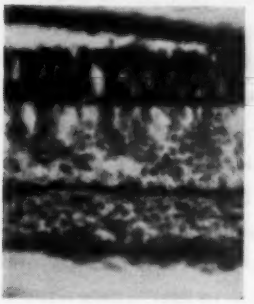


Fig. 2 Choline staining of the light adapted retina of chicken(visual cell layer and external reticular layer)

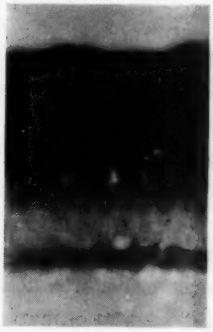


Fig. 3 Choline staining of the dark adapted retina of chicken (visulal cell layer and external reticular layer)

Fig. 4 Choline staining of frog's retina

Fig. 5 Choline staining of light adapted retina of the frog after acetylation

Fig. 6 Visual cell layer of Fig. No. 5

Fig. 7 Choline staining of the light adapted retina of the frog after applying anilin chloride

Fig. 8 Visual cell layer of Fig. No 7

Fig. 9 Choline staining of the light adapted retina of the frog after bromination

the point of Hg ion of complex salt because bromate has a strong binding ability as one of the halogens, therefore the choline staining becomes negative in both of the light and dark adapted retinas.

It has been believed, that anilin chloride blocks free aldehyde. This author applied this fact on the choline substance and saw no fine black granules but noted rough black granules disseminated in a part of the light adapted retina of the frog. The staining of PAS reaction tends to decrease slightly in the whole layer, including the visual cell layer.

Much of the reaction of anilin chloride still remains unknown. It might be resulted from a reaction of chloride as one of the halogens that the choline staining decreases or disappears also.

From the facts described above it is concluded that the so called choline substance which Hirose found in the visual cell, reticualr and nuclear layers has something which is blocked by acetylation, bromination and aniline chloride; and it is assumed indirectly, from the result of the blocking test, that the so called choline substance contains choline, lecithine and acetylcholine.

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ON THE OPERATION "PERNASAL METHOD" IN TUMOURS OF PITUITARY REGIONS WITH SERIOUS DISTURBANCE OF VISION

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Introduction

The treatment of tumours developing in the pituitary gland and its surrounding regions, which are situated at the deepest position of the cranial cavity, even though most of them are good natured, has been one of the most interesing operations by a large number of surgeons, since the dawn of cerebral surgery. For plenty of strange

symptoms often appear, because of the fact, that the pituitary gland holds the highest rank of the whole endocrine system and is the organ which always controls and regulates them and that the region neighbors the optic nerve, chiasma and the brain stem which is called the center of the autonomous nerve system. As for surgical treatment of them, the two kinds of methods with entirely different courses, namely the trepanation and "pernasal method", haven been devised, and after much meanderings, the great efforts which have beenmade on the controversies between both of them, have naturally brought about much progress of the operative methods. With the latest development of antibiotics, the results of operation have so markedly advanced, that we are much impressed with them.

At present, the extirpation of tumours of these regions, is usually performed by the cranial method, which has a wide range of indication, and the "pernasal method" is considered the special technique of a few otorhinolaryngologists. Takahashi, one of the authors has more improved Hirsch's method "perseptal method", which had already given much progress of the nasal method, and then it has been possible to enlarge the operative field. The operation was at first carried out in 1949 and then, after experience, the results have gradually been raised. Particularly, in several cases of recent time, the intracapsular total-extirpation has also been possible. The results of the operations of all 16 cases, or 19 times till now, and some comment about them and the comparison with the trepanning method, will be expressed in the present paper.

Improved Operative Method "via Nasal Septum"

O. Hirsch publisched in 1910 and 1912 the resuts of his originated endonasale method "perseptal, transsphenoidal". This first operation was based on the opening of one sphenoidal cavity by the ethemoidal route (M.Hajek). After the publication of this excellent method, not to mention the rhinologists at that time, the neurosurgeons also tried to follow this and obtained such good results as had never been seen. Even Cushing, Frazier and other, who were the authorities on cerebral surgery, once asserted that the nasal method was superior to the cranial (trans-frontal) method. Improving Hirsch's method, R. Takahashi, one of the authors, practised his way in each case, and confirmed the superiority of the method "via nasal septum". This way is separated in the following 3 stages.

Improved perseptal method. A. Enlargement of nasal cavity. B. Management of nasal septum and sphenoidal sinus. C. Intracranial management

The enlargement of the nasal cavity is the preparatory operation in order to make the operative field wide for intracranial management and also the prevention against post-operative infection. The patient is put into a half sitting position, and under local anesthesia with 10% cocaine hydrochloride, the cellules of the bilateral ethemoidal sinus are intranasally opened, as completely as possible, without any injury of concha nasalis. At that time, the extensive removing of the fore wall of the sphenoidal sinus

is desirable. In case of inflammation of the accessory sinus, its radical treatment should simultaneously be performed. Next, the inside wall of ethmoid cellules, namely the concha wall, is bended, and dislocated to the outside, as much as possible, with complete or incomplete fracture of concha nasalis, and then the olfactory fissure is extensively enlarged and, not to mention the natural orifice of the sphenoidal sinus, its fore walls are also exposed. When the patient is strong and has no inflammation of the paranasal sinus, the next stage may successively be performed, but in the consideration of charge of patients, the practise of the second stage is better to be carried out after about 2 weeks. For the purpose ofthe lateral pressure and fixation of concha, the gauze rubbed with the ointment (ferro chloride 2%, calcium chloride 3%, homosulfamine 7%, vaseline 88%) is used for tamponade and is removed after 2—3 days. The operative healing of inflammation of the paranasal cavity is necessary by all means, the prevention against post-operative infection, and the lateral disolcation of concha walls at the same time is the most important point of this improved method.

Next, the submucous resection of nasal septum (fensterlike extirpation) is practised Simultaneously, the medial plate of the ethmoid bone and vomer are removed as extensively as posible, and the rostrum of the sphenoid bone at the posterior part. Thus, when a long rhinoscope is plunged between both the mucous membranes of the nasal septum and is opened somewhat intensively, the operative field, as wide as about two times of an one sided nasal cavity, can be obtained. After the rostrum of the sphenoid bone and the intersphenoid-septum are removed with Hajek's rongeurs, chisels and others, the heaving part toward the sella turcica of sphenoid cavity appears. At this management, the oppression of the concha walls to the lateral side at the first stage is significant. The posterior wall of the sphenoidal sinus is often being lifted up or thined by the pressure caused by the pituitary tumours, and the sinus is becoming narrow. Sometimes the posterior wall of the sphenoidal sinus is being destroyed by the tumour and the periostum of the sella(dura)are being swollen into the sphenoidal sinus through the defect part. Therefore, it is important to probe, with a pretty long sound the resistance, hardness and width of the posterior wall of the sphenoid cavity, comparing it with the X-ray findings. If the posterior wall is hard, it is tangentially scraped with a woodhandled chisel. The bluish colored dura periosteum becomes exposed. The pulsation of the internal carotid is observed in a lateral position, and the scraping to this direction should cautiously be carried on. The exposure measures about 1.5 by 1.75 cm, more or less, depending upon the size of the enlarged sella.

Thus, the third stage, intra cranial management is next performed. The field of operation can be kept free of blood by suction. R. Takaoashi designed a series of operative apparatus for this purpose. The operative field is always, with a fluid streaming apparatus, washed by half-heated physiological saline soltion and wate-soluble penicillin, and an electric coagulator, a bleeding-stop-page crip and cotton immersed in physiological saline solution are used for bleeding stoppage, cleaning and pressure

while the whole process of operation. The nasal method, compared with trepanation, has almost no danger of brain compression, shock and so on, and then the operation should leisurely be done, without haste.

After the complete exposure of meninges, some proof-punctures with negative pressure should be carried out from several spots, to search how deeply the tumour exists in the sella turcica or outside of it, and whether the tumour is cystic or parenchymatous. If the situation of tumour is known, toward that direction, and if indistinct, downwards from the middle point of the meninges, a longitudinal incision is carried on If the tumour is cystic or potagelike, its contents are completely removed with the stream of the solution, and if parenchymatous, a small curette is thrusted into the wound, to scrape the contents out quietly, namely "Excavation or Excochleation". In cases of some other kinds of tumours, the contents can be extirpated by this management (manipulation), as if a half-boiled egg is scooped out. And if the tumour is soft, it can be removed to greater or less extent by suction. In case of a cyst, when some photographs construct filling are taken, after puncture-suction, it is easy to recognize

Table 1

Case No.	Name	Diagnosis	X-ray Findings of Salla Turcica and Dorsum Sellae	Findings of Eye-Ground (disk)
1	K.K. 35	Adenoma	enlarged Dilation of Orifice	Congestion
2	K.M. 42	Craniopharyngioma	indistinctness Cloverform shadow	inflammative atrophy axial atrophy
3	G.Y. 37	〃	Transfiguration of Dorsum Sellae	slightly Congestion Congestion
4	A.N. 47	〃	Calcification Transfiguration	〃 pallor
5	Y.M. 45	〃	Disapearance Calcification	〃 〃
6	S.I. 54*	Chromophobe Adenoma	Complete Distruction of Dorsum Sellae	anemic pallor
7	T.Y. 47	Glioma	Disapearance Irregularity	almost normal 〃
8	H.T. 10	Adenoma	Swelling Disapearance	pallor
9	T.A. 56	Atr. N. Opti. Chrom. Adenoma	Dicalcification of the floor	〃
10	S.O. 23	Neuritis retrobl. Adenoma	enlarged thinness	Discoloration
11	S.A. 58	Cyst. Adenoma	enlarged Disappearance	total paller
12	T.M. 53	fibriblast. Meningioma	〃 〃	pallor Discoloation
13	Y.I. 21	?	complete Disappearance	pallor
14	K.I. 44*	Hemangioma	enlarged Dissppearance	anemic slightly pallor
15	M.K. 47*	Cnromophobe Adenoma	enlarged Distruction	pallor
16	Y.S. 23	〃	〃 Dilation of Orifice	〃

* Re-operation

the range of tumor. If the orientation is difficult because of bleeding and other reasons, the operation may, at once, be suspended and be performed again after 2—3 weeks. The fact, that the re-operation is possible and easy, is one of the most characteristic matters of the pernasal method.

Antibiotics are given on the day before the operation, and administration is continued for about one week after the operation.

Cases. Sixteen cases received the improved method "via nose" and, in 3 of them, the re-operation has been carried out. Now, omitting detailed expressions, the author showed the resume of all the cases, in the following table.

The author will make some investigations, synthesizing all these cases.

i) Kinds of tumors. While there are many kinds of tumours developing in the pituitary gland and its surroundings, 7 of the present 16 cases, were adenoma. The chromophobe adenoma, which is called to be the most numerous, was histologically confirmed in 4 cases (No. 6,9,15 and 16). The other 4 cases were all cystized and the kinds of adenoma could not be determined. Craniopharyngioma was represented 4 cases, which were apt to be cystized. No. 3 has already been cystized. In 2 of them (No. 4 and 5), calcification findings within the region of the sella on X-ray photograph were demonstrated. Hemangioma, like in No. 15, was an extremely rare kind, and the re-operation succeeded in the intracapsular total-extirpation.

2) Symptoms. Main symptoms caused by the tumours of the pituitary regions are divided into the opthalmological ones and the ones of the rise of intracranial pressure and of disturbances of endocrinous organs. In chromophobe adenoma and craniopharyngioma, which were most of the controls of surgical operation, the oppressive symptoms to the neighborings organs, especially the syndroms of optic chiasma and rise of intracranial pressure, were main symptoms. The present cases, complaining of visual disturtances and head-heaviness feeling or headache, as initial symptoms, all visited ophthalmologists, and next were introduced to us, otorhinopharyngologists.

i) Eye symptoms: As to the ocular symptoms caused by cerebral tumours, there are, generally, disturbances of of visual acuity, visual field, eye-ground, pupil and oculomotor. On visual acuity, the present cases were divided as follows: blindness or light sense of bilateral eyes in 3 cases, blindess or light sense of unilateral eye in 4 cases: both the numbers were counted on a half of all the cases. Only on the standpoint of this visual acuity, the time of operation was considered to be too late in the present cases.

It is well known, since the former days, that the change of visual field showed various findings (bitemporal hemianopsis), due to the region and direction of the pressure caused by the pituitary tumour, to optic nerve and chiasm. Beginning encroachment upon the chiasma manifests itself by slight temporal restriction of the field for colors or by central scotoma. These field defects may progress with the growing tumour to the point of loss of the temporal quadrant on one or both sides, and later to temporal

or bitemporal hemianopsia: finally, one quadrant on each side may remain from the visual field, or blindness of one or both eyes may result.

Examining the present cases on such a point of view, we can find that the cases with bitemporal hemianopsia or narrowness of visual the field were the cases, whose chiasma fibers were damaged at the central part of the optic chiasma, and in five cases, namely No. 3,9,10,11 and 16, such a change of visual field was observed. They were all adenoma and craniopharyngioma. The cases with bitemporal hemianopsia, which had been seen at a somewhat earlier time, and absolutely defect in the superior region and relatively in inferior, were never found. However, in the earlier period, namely in the so-called initial symptoms of hypophisial tumours, the defect or narrowness of the visual field in bitemporal superior regions, was observed in the left eye of No. 12 and in the post-operative convalescent stadium of No. 6. The blindness in the unilateral eye and temporal hemianopsia in the other eye, show the disturbance of the more lateral region than that of optic chiasma. Such a phenomenon was demonstrated in the convalescent stadium of No. 6 and 14, and, moreover, in the pre-operativ stadium of No. 11, the bitemporal hemianopsia progressed and the visual field remained only in binasal superior regions (q.v. the table of visual field).

As for the eye-ground findings, the outline was expressed in the table. About the other ocular symptoms, slight exophthalmos was observed in No. 2 and 13, and the diplopia caused by the paresis of oculomotor nerve, as an initial symptom, was found in No. 1 and 3.

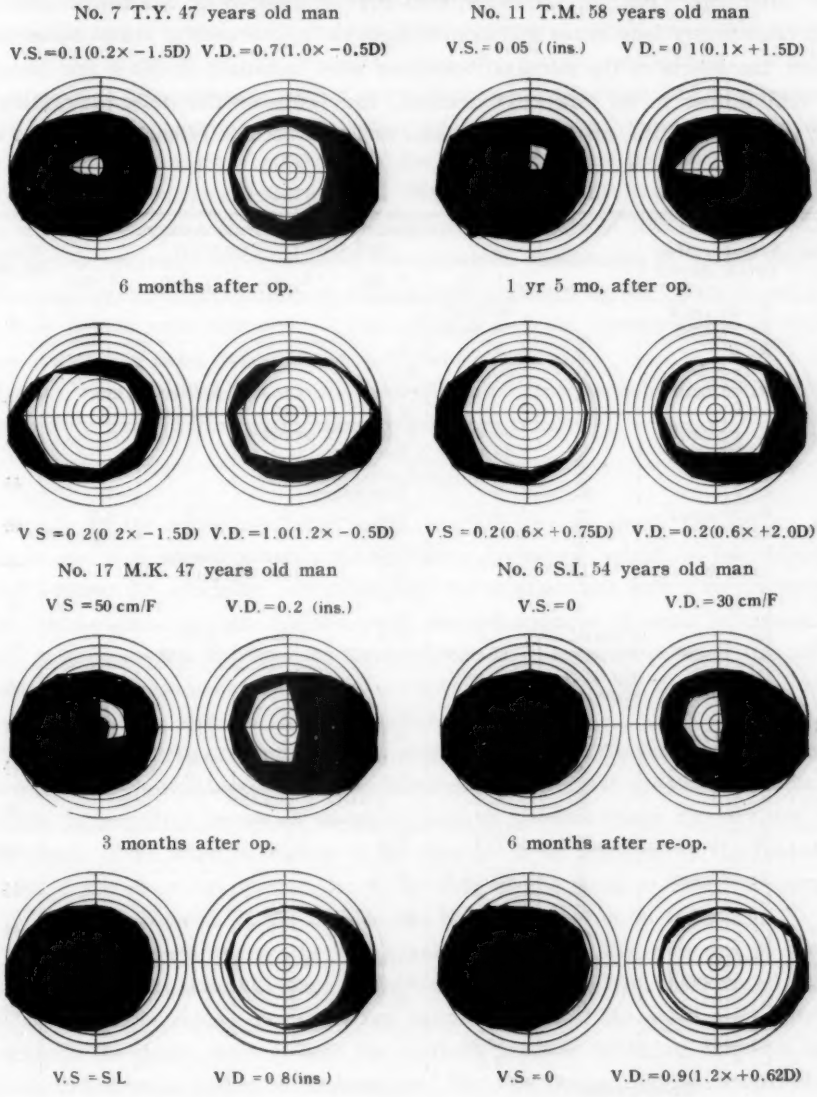
ii) Rise of intracranial pressure: Besides or with the abovementioned ocular symptoms, which were the most important ones as initial symptoms, head-heaviness feeling or headache were complained of, in various degrees, in each case. The pressure of cerebrospinal liquid at the admission time, was normal only in No. 7 and 15, but in all the other cases, the pressure was moderately or intensively increased, and in No. 1,2,8 and 13, it reached to about 500mm H_2O (at side lying position).

iii) Endocrinological Findings: In cases of hypophisial tumours, the secretion of hormoes of gonadotropin system is stopped before the other hormones: thyrotropin system is the next and ACTH. is the hardest to be influenced. The adenoma of the pituitary gland developes in the sella turcica, and sometimes presses and destroys the posterior wall of the sphenoidal sinus, and it develops through the orifice of the diaphragm of of sella, and presses the optic chiasma. Therefore, in the consideration of time process, further before the appearance of visual disturbance, the sexual disorders due to the lack of hypophisial hormone, especially gonadotropin-system hormone, undoubtedly, begins to be raised, even though slowly. Among the present cases, No. 3,6,9,15 and 16 complained distinctly of impotence or menstrual disorders. In almost all the other cases with intensive visual disturbances, panhypopituitarism or Simmond's syndrome were, of course, observed, as shown in plenty of text-books. Hypomyotonia, enfeebleness feeling, inactivity of action, dropping of hair and pubic hair, delicacy or

waxlike paleness of skin, impotence, menstrual disorder or amenorrhoea, fall of basal metabolism, adiposis trend in few cases and so on were observed.

The atrophy of the pituitary gland, due to the long time pressure of the tumour, and the above-mentioned hypofunction of hypophysis, owing to the operative stress, can be somewhat restored after operation, but the effects are almost hopeless, even

Fig. 1. Visual Fields of Patients before and after the Operation


No. 7 T.Y. 47 years old man
V.S.=0.1(0.2×−1.5D) V.D.=0.7(1.0×−0.5D)
6 months after op.
No. 11 T.M. 58 years old man
V.S.=0 05 ((ins.) V D.=0 1(0.1×+1.5D)
1 yr 5 mo, after op.
V S =0 2(0 2×−1.5D) V.D.=1.0(1.2×−0.5D)
V.S =0.2(0 6×+0.75D) V.D.=0.2(0.6×+2.0D)
No. 17 M.K. 47 years old man
V S =50 cm/F V.D.=0.2 (ins.)
3 months after op.
No. 6 S.I. 54 years old man
V.S.=0 V.D.=30 cm/F
6 months after re-op.
V.S =S L V D =0 8(ins)
V.S =0 V.D.=0.9(1.2×+0.62D)

with the pharmaceutic compensation of the present time, as pointed out already many years ago. The cases who, after operation, recovered their healthy condition and vital energy, were only three No. 6, 11 and 12.

Results of Operation and Prognosis

The results achieved by the pernasal method in the treatment of pituitary tumors deserve attention. But all the cases, who were introduced by ophthalmologists, had gone through pretty long years and months since the appearance af visual disturbances, and then the effects of the pernasal operation were indistinct in not a few cases As to the skillfullness in the operative method, the intracapsular total-extirpation has become possible and the results of operation has also become remarkable in the cases

Table 2

Case No.	Pre-operative Visual Acuity	Op. Method	Post-operative Vtsual Acuity and General Prognosis					Effect of Op.
			1. mo.	3. mo.	6. mo.	lyr. 6 m.	3. yrs.	
1	R: 50 cm/F L: 25 cm/F	Improved Perseptal Method	50 cm/F 25 cm/F					+
2	R: 0 L: s.l. 1.		0 s.l.	0 s.l.				−
3	R: 50 cm/F L: 0			0.5 0	0.7 0.15	∫ after 20 mo. Cachexy		++
4	R: 50 cm/F L: 20 cm/F		50 cm/F 20 cm/F	† after 2 months Cachexy				−
5	R: 0 L: 0		0 0	† after 3 mohths Pneumony				++
6	R: 30 cm/F L: 0		0.5 0	0.5 0	0.6 0	0.7 0	0.7 0	+++
7	R: 0.7 L: 0.15			1.04 0.0	† after 6 months from bleeding			+
8	R: 0 L: 0		0 0					±
9	R: 0.7 L: 2.5m/F	Cranial M. Perseptal	0.8 30 cm/F	0.8 30 cm/F	0. 9 30 cm/F	1.0 30 m/F		++
10	R: 2 m/F L: 1 m/F	Op. of N. opt Cranial M.	2 m/F 0					±
11	R: 0.2 L: 0.12	Improved Perseptal Method	0.1 0.1	0.1 0.1	0.1 0.1	0.2 0.2		+++
12	R: 10 cm/F L: 0.6		20 cm/F 0.4	1 m/F 0.8	1 m/F 0.8	0.04 1.0		++
13	R: s. 1. L: 0		s. 1. 0	† after 6 months spinal Rhinorrea				+
14	R: 0.7 L: 0		0.9 0	0.9 0	1.0 0			+++
15	R: 30 cm/F L: 0		50 cm/F 0	0.02 0				++
16	R: 50 cm/F L: 0		0.02 0	50 cm/F 0				++
17	L: 0.15 L: 50 cm/F		1.2 20 cm/F	1.5 20 cm/F	0.3 0			+++
18	R: 0.02 L: 0		0.8 0	0.5 0				+++
19	R: m.m. L: 0.1		m.m. 0.2					±

( ) : Re-operation

of the latest time. The post-operative recovery of visual acuity was expressed en bloc in the table, while the visual field has been dilated, in the proportion to the former.

In case of trepanation, the pre-operative visual acuity inferior to 0.1, is considered impossible to be recovered, but the most effected one of the present cases by the septal method was restored to 0.9 at 30cm/F in the unilateral eye. Several cases were restorerd to about 0.5 at 50cm/F (q.v. the Table II).

If the tumour had been cystic and the residual part had been left at the time of operation, the loss of visual acuity and the other oppressive symptoms would sometimes appear, as the increase of the contents. But the simple management, to suck the contents through the posterior wall of the sphenoidal sinus which had been removed at the first stage of operation, could restore again the original visual acuity in several cases. This matter may be called one of the characteristics of the nasal method, which has been impossible in the cranial method. However, naturally, the cases whose visual acuity is nil or near to nil, can never be restored. In spite of that, as in No. 3,6 and 18, the earlier operation brought about the wonderful restoration of visual acuity.

The post-operative irradiation of radium was practised in No. 7,8 and 9, and cosiderably good results were obtained. This is also one of the characteristics of the nasal method, which has been impossible in the cranial method.

Finally, the tumour remnants must be prevented from growing and this goal can be reached by local radium application or by X-ray treatment.

Discussion and Conclusion

Through all the above-mentioned cases, whether in the nasal method or in the improved one, it is considered that the operative technique might be too difficult for any one without the specialist otorhinologists, but it needs not such a special technique for the rhinologists who are familiar with the management of usual intranasal operations. It is necessary, however, to make efforts for the acquirement of the ability to take emergency management, in accordance with the condition of the tumour, in intracranial manipulation after incision of the dura mater.

When the tumour is expanded to the cutside of the sella turcica, the cranial method is, of course, more advantageous than the nasal method, while to the tumour in the sella, the latter is benefitial, by which the extirpation is possible under direct vision of the tumour itself. Even when the tumour is too gigantic to be removed by the trepanation, like in No. 5 and 13 of the present paper, there is, in the nasal method, the advantage that the cranial extension of the tumour can be changed to nasal extension.

Till now, the mortality rate of the cranial method in the tumours of pituitary regions, is 5—10% in general. One author reported that he had experienced no death in several dozens of cases. On the other hand, the rate of the nasal method is about 5%. Though the death rates of both the methods are now declining, it seems that the death rate is somewhat higher in trepanation. For this reason, indeed, the trepanation

has the possibility of taking emergencey treatments under direct vision of thə optic chiasma and other important organs, but when the tumour is mainly situated in the sella turcica, the nasal method should absolutely be applied, because of the easiness of technique and of less danger.

O. Hirsch reported in 1956 that of his 65 cases (12 with craniopharygioma and with cranial extension) in the antibiotic era, only 1 died—a mortality of 1.5%, and a nineteen year follow up study revealed, that 68 percent of the patients showed improvement lasting for 5 to 19 years. A rotational type of X-ray treatment, using a 2,000,000 volt machine, was introduced by Trump, Wright, Evans, Harre and Lippincott in 1951.

From the experiences of 19 cases of the improved method "via nose" in tumours of hypophysial regions, which had considerably developed, the authors obtained the following conclusion.

1. In the method "via nose", compared with the trepanation, the technique is easy, the operation time is short, the bleeding quantity is less, the charge of the patient is light, the operative field can be enlarged by the dilating management of the nasal cavity, and it is not so narrow that the operators of trepanation have to be anxious about it.

2. As far as the tumour existed mainly in the sella turcica, however gigantic it is, the intracapsular total-extirpation is possible. Perhaps, the larger the tumour, the more difficult is the cranial method.

3. In the method "via nose", the re-operation is not only possible, but further easier than the first operation. To the tumour remained because of danger at the time of operation, the direct and repeated use of radium is possible. At the relapse, due to the increase of cystic contents, the puncture and suction are also possible in many a time.

4. Of the gigantic tumour of this region, which is beyond the indication of trepanation, it is possible to change its cranial extension to the nasal extension and to mitigate the clinical symptoms. (Trans-sphenoidal Decompression)

5. Cerebral edema, as a complication at trepanation, shock at operation, postoperative disturbances of diencephalon, especially hyperthermia (hypothalmic crisis), spiritual disorder, and so on, have never been experienced till now. However, after operation, slight meningismlike symptoms were found in 2 cases, but they were temporary and were soon healed. The danger of infection from the nose, is further less than expected, because of the use of antibiotics.

6. In the experience of 16 cases, the extension of the tumour to the sphenoidal sinus was observed in 7 cases, who were unexpectedly large in number, and then the importance of the method "via nose", in tumour of these regions, should be recoguized.

7. There has been no case up to date, in which the direct cause of death was due to this cperation. Five cases have died in the process till now after operation.

8. The prognosis of visual acuity and visual field has beed satisfactory, provided that the optical fascicular atrophy was not remarkable and the tumor was non-malignant. Most of the patients of this disease, visit, at first, ophthalmologists, due to their initial symptoms, and then the diagnosis at a ophthalmological institute is very important. Authors feel keenly that, if the operation had been performed at an easier time, it would be possible to make their prognosis as reaching further than the abovementioned.

Concerning the therapy of ocular disturbance caused by pituitary tumours, the endonasal method proved to be more easier and effective and demonstrated a more stisfactory prognosis compared to the cranial method provided that the tumour was located in an intra-sellar position.

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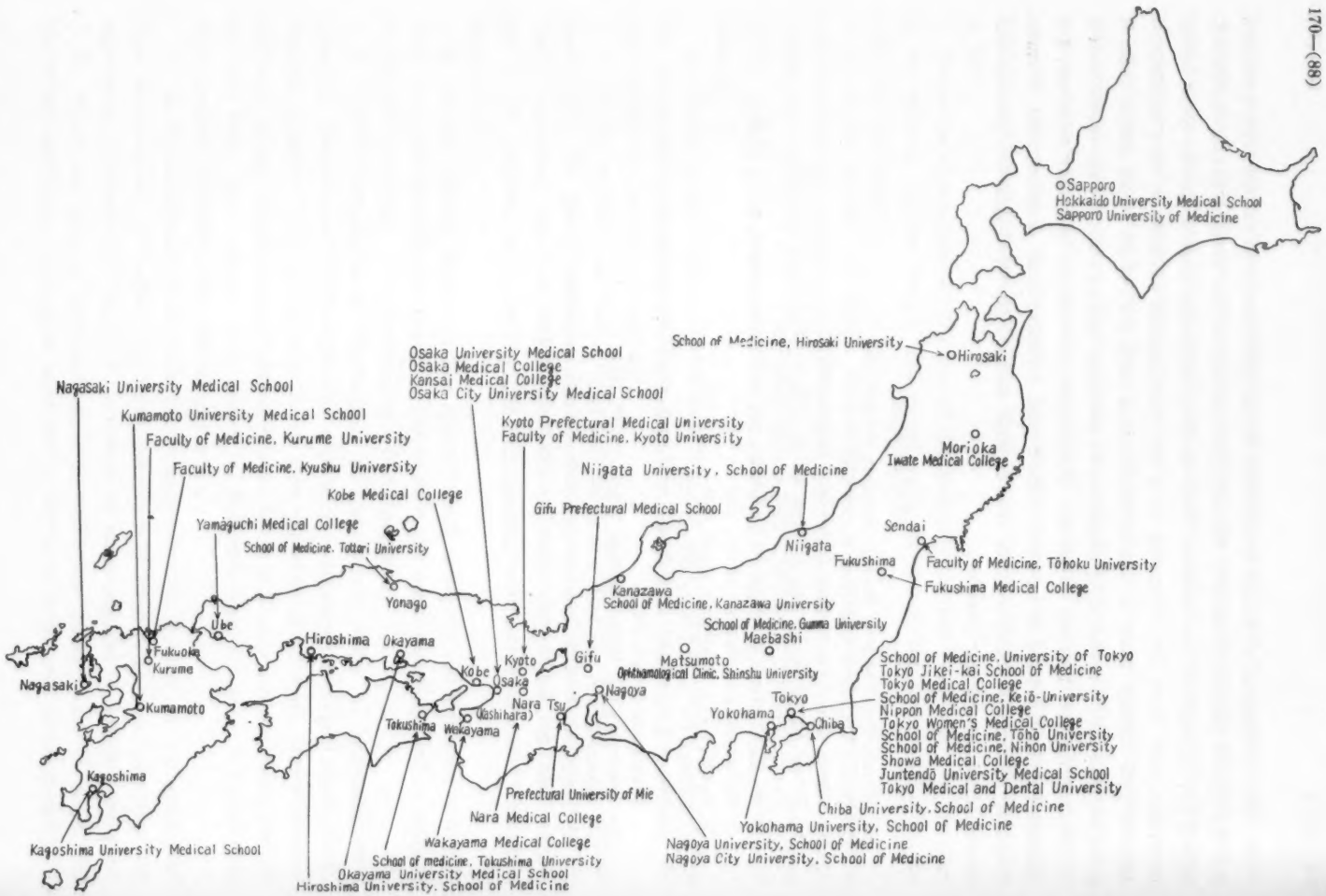
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